For Protocol Amendment #03 to: NRG-GY027
NCI Protocol #: NRG-GY027
Local Protocol #: NRG-GY027
NCI Version Date: 12/22/2023

SUMMARY OF CHANGES

Response to Comments Received 12/13/2023.

Comments Requiring a Response – Major Issues:

#	Section	Comments
1	Cover Page For Regulatory Submission	Please replace the following with the latest CTSU template 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 the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance. Please revise the excerpt below as indicated. The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website CTSU Regulatory Support System (RSS). **PI Response: This change has been made.**
2	2	Please update the background to indicate the experience with the dose escalation and provide support for the dose selected for expansion. **PI Response: Section Now reads:** **There have been 12 participants enrolled and treated on DL1 (200mg) and DL2 (300mg). Among these 12 eligible and treated participants, 11 have been off study treatment.** **Dose Level 1 had two cohorts with 7 patients enrolled and treated including 6 patients who were considered DLT-evaluable. Among these 6 DLT-**

#	Section	Comments
		evaluable patients, 1 had DLT based on treatment discontinuation > 14 days due to grade 3 maculo-papular rash. **For Dose Level 2, there were five patients in two cohorts with two DLTs. The DLTs were grade 2 diarrhea and grade 4 neutropenia. There was another participant during the postoperative period with a SAE for prolonged apneic arrest with anoxic injury. There were no delays in reaching surgical intervention in either DL1 or DL2. The MTD was determined to be 200mg daily.**
3	6.3	This section suggests that a maximum of 2 dose level reductions can occur for ipatasertib, however, there is only one dose level described in the protocol. Please clarify the statement to only allow 1 dose level reduction is permitted or clarify the permitted dose reductions. **PI Response: Given the MTD is at DL1 of 200mg daily, there will be only one dose level reduction to 100mg daily.**
4	8, Registration and Study Entry Procedures	Please replace the following with the latest CTSU template language. 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 Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability. RCR utilizes five person registration types. Investigator (IVR) — MD, DO, or international equivalent; Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD); Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems. RCR requires the following registration documents:

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>
<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>
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.
Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.
PI Response: The section is now up to date.
</td></tr>
<tr><td>5</td><td>8.1, Cancer Trials Support Unit Registration Procedures</td><td>Please replace the following with the latest CTSU template language.
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</td></tr>
</table>

#	Section	Comments
		(SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878). In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record: Have an active CTEP status; Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) on at least one participating organization's roster; If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record; Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and Have the appropriate CTEP registration type for the protocol. Additional Requirements Additional site requirements to obtain an approved site registration status include: An active Federal Wide Assurance (FWA) number; An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and Compliance with all applicable protocol-specific requirements (PSRs). **PI Response: Section has been updated.**
6	8.1, Cancer Trials Support Unit Registration Procedures	The following paragraph can be deleted, as it is not a Protocol Specific Requirement. Protocol-Specific Requirements for Protocol NRG-GY027 Site Registration Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen, and may need to answer additional questions related to treatment in the eligibility checklist. **PI Response: This has been deleted.**
7	8.1, Cancer Trials Support Unit Registration Procedures	Please replace the following with the latest CTSU template language. 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

#	Section	Comments
		investigators and staff on a participating roster. To view/download site registration forms: Log in to the CTSU members' website (https://www.ctsu.org); Click on Protocols in the upper left of the screen: Enter the protocol number in the search field at the top of the protocol tree; or Click on the By Lead Organization folder to expand, then select NRG, and protocol number NRG-GY027. Click on Documents, Protocol Related Documents, and use the Document Type filter and select Site Registration to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.) **PI Response:** Section has been updated.
8	8.1, Cancer Trials Support Unit Registration Procedures	Please revise the excerpt below as indicated. 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 at 1-866-651-2878 in order to receive further instruction and support. **PI Response: Section has been updated.**
9	8.1, Cancer Trials Support Unit Registration Procedures	Please revise the excerpt below as indicated. 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 include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List. **PI Response: Section has been updated.**
10	8.2.1, Oncology Patient Enrollment Network	Please revise the excerpt below as indicated. A valid CTEP-IAM account; Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; Please revise the excerpt below as indicated.

#	Section	Comments
	(OPEN)	All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) HIPAA authorization form (if applicable) Please revise the excerpt below as indicated. Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with patient enrollment the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study. **PI Response: Section has been updated.**
11	10.3.2.2 & 10.3.3.2	WES and RNAseq through the NCLN may be performed at either the NCLN Genomics Laboratory or the MoCha, Frederick National Laboratory for Cancer Research (FNLCR). Please update the update references to the "NCLN Genomics Laboratory" in Sections 10.3.2.2 and 10.3.3.2 to list both laboratories: "NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR)". **PI Response: Sections have been updated.**
12	12.4, Rave-CTEP-AERS Integration	Please replace the following with the latest CTSU template language. 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. Include the following highlighted paragraph about pre-treatment AEs only if the study requires reporting of pre-treatment AEs and the CTSU standard Pre-Treatment AE form is used. Pre-existing medical conditions are not considered adverse events and therefore should not be reported on the Pre-Treatment Adverse Event form. Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form. Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened condition should be reported in Rave as a routine AE. Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start

#	Section	Comments
		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. **PI Response: Section has been updated.**
13	12.5, Data Quality Portal	Please replace the following with the latest CTSU template language. 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

#	Section	Comments
		Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules. CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website. To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules. **PI Response: Section has been updated.**
14	12.1, Data Management/ Collection	Please replace the following with the latest CTSU template language. 12.1 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: Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements: Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type; Rave Investigator role must be registered as 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. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically

#	Section	Comments
		granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the Tasks pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the Studies pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will replace the eLearning link under the study name. No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave resource materials (Medidata Account Activation and Study Invitation). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response: Section has been updated.**

#	Section	Comments
1	Title Pages	• NCI Version Date is now 12/05/2023 • The schema has been revised to reflect the determind MTD.
2	5.1	Dose escalation table has been modified to highlight the established MTD. A note has been added below the table regarding the opening of the expansion phase.
3	5.5, 5.6, 13.1	"The dose escalation phase indicated Dose Level 1 as the MTD. Based on the safety data review by the study team and CTEP, patients enrolled to the expansion phase will be treated at Dose Level 1 (See Section 5 Table 1)" has been added to 5.5., 5.6, and 13.1.
4	10.3.2.2, Appendix VII	Updates have been made to the biospecimen processing and storage process at the EET Biospecimen bank.
5	ICD	See ICD for changes.

NRG Oncology
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Philadelphia, PA 19103
Nrgoncology.org

NRG-GY027: PHASE I/IB SAFETY AND PHARMACODYNAMIC STUDY OF NEOADJUVANT (NACT) PACLITAXEL AND CARBOPLATIN WITH IPATASERTIB AS INITIAL THERAPY OF OVARIAN CANCER
PTMA 100805

ClinicalTrials.gov Identifier NCT#05276973 IND#160809
NCI Version Date: December 22, 2023

Principal Investigator:
Katherine Fuh, MD, PhD
University of California San Francisco
Division of Gynecologic Oncology
San Francisco, CA 94143
[redacted]

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

NRG Oncology Participating Institutions	
AZ017	Banner University Medical Center -Tucson
CA249	UC San Diego Moores Cancer Center
CA824	University of California San Francisco
CO070	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
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

Protocol Agents:

Agent	Supply	NSC#	IND#	IND Sponsor
Paclitaxel	Commercial	125973	160809	CTEP, DCTD
Carboplatin	Commercial	201345		
Ipatasertib	Genentech, INC.	781451		

Document History	
Amendment 3	**December 22, 2023**
Amendment 2	August 07, 2023
Amendment 1	April 24, 2023
Initial	May 11, 2022

STUDY TEAM

PRINCIPAL INVESTIGATOR	STATISTICIAN
Study Principal Investigator Katherine Fuh, MD, PhD University of California San Francisco Division of Gynecologic Oncology San Francisco, CA 94143 [redacted]	[redacted] PhD NRG Oncology Statistics and Data Management Center Buffalo, NY [redacted]
MODALITY CHAIRS	
Study Co-Chair/ [redacted], MD Stephenson Cancer Center Oklahoma City, OK 73104 [redacted]	Translational Science Chair [redacted], PhD Beth Israel Deaconess Medical Center Boston, MA [redacted]
MODALITY CHAIRS Con't	
[redacted], PhD, MPH NRG Oncology Philadelphia, PA [redacted]	Research Nurse [redacted], BSN, RN Georgia Cancer Center/Clinical Research Unit Augusta University Augusta, GA [redacted]
Developmental Therapeutics Chair [redacted] MD New York, NY [redacted]	

STUDY-SPECIFIC CONTACTS AND RESOURCES	
For questions/comments related to:	**Contact:**
Protocol Document, IRB review, informed consent documents and amendments	[redacted], Protocol Coordinator NRG Oncology [redacted]
Data Management	[redacted]

Including submission, eligibility	NRG Statistics and Data Management Center - Pittsburgh [redacted]
Biospecimen Collection	EET Biobank 614-722-2865 bpcbank@nationwidechildrens.org
Regulatory	NRG-GY-Regulatory@nrgoncology.org
NRG Oncology Gynecologic Oncology Chair	[redacted], MD Memorial Sloan Kettering Cancer Center New York, NY [redacted]

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

TABLE OF CONTENTS

NRG-GY027
SCHEMA

Women with stage III/IV high grade serous or grade 3 endometrioid ovarian cancer undergoing neoadjuvant chemotherapy (NACT)

Pre-treatment formalin-fixed, paraffin-embedded (FFPE) tumor block collected from laparoscopy (preferred) or five 18G cores (embedded in one block) by radiology/interventional radiology (acceptable) must be available for submission.

Neoadjuvant Chemotherapy (NACT)
Paclitaxel 175mg/m2 + Carboplatin AUC 5 + 200 mg Ipatasertib* po daily
Every 3 weeks x 3 cycles

Followed by single-agent ipatasertib daily until 24 hours prior to Interval Debulking Surgery (IDS) within 6 weeks of Cycle 3, Day 1

Tissue collection at the time of IDS, to be collected from anatomical site similar to pre-treatment tissue procurement (if possible).

NOTE: Post-operative paclitaxel/carboplatin will be given as per usual care. Dates and doses of post-operative paclitaxel/carboplatin treatments will be collected.

* The Maximum tolerated dose was determined to be 200 mg for ipatasertib. As of December 22, 2023 the trial is now open to the dose expansion phase only. **(22-DEC-2023)**

1. OBJECTIVES

This Phase I/IB trial aims to evaluate the pharmacodynamic and pharmacokinetic endpoints for the use of ipatasertib in combination with paclitaxel and carboplatin in newly diagnosed stage III/IV ovarian cancer.

1.1 Primary Objective

1.1.1 To estimate the maximum tolerated dose (MTD) and the dose limiting toxicities (DLTs) of ipatasertib in combination with paclitaxel and carboplatin as neoadjuvant chemotherapy for ovarian cancer

1.1.2 To determine the feasibility of the treatment regimen once the MTD is estimated.

1.2.3 To assess the toxicities of ipatasertib in combination with paclitaxel and carboplatin by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

1.2 Secondary Objectives

1.2.1 Objective response rate by RECIST 1.1 prior to IDS.

1.3 Translational Research Objectives (24-APR-2023)

1.3.1 To evaluate the change of pPRAS40 expression in the pre-treatment tumor vs. on-treatment tumor. (Exploratory)

1.3.2 To identify the pharmacokinetics of ipatasertib in the tissue and blood. (Integrated)

1.3.3 To correlate antitumor response with genomic alterations in PI3K Pathway genes (PTEN, PIK3CA, PIK3R1, AKT1, p53 loss, KRAS, NF1, TSC1/TSC1). (Integrated)

1.3.4 To correlate antitumor response with transcriptomic alterations in PI3K Pathway genes (PTEN, PIK3CA, PIK3R1, AKT1, p53 loss, KRAS, NF1, TSC1/TSC1). (Integrated)

1.3.5 To correlate response with PTEN loss. (Integrated)

1.3.6 To correlate phosphorylated AKT S473 and T308 with response to ipatasertib as neoadjuvant chemotherapy for ovarian cancer. (Exploratory)

2. BACKGROUND

Neoadjuvant chemotherapy (NACT) is standard of care for approximately 50% of patients with advanced stage ovarian cancer and provides a unique ability to collect paired tissue (Knisely *et. al.*, 2020). Even though the initial response is 80%, the majority will relapse and die from disease. Improving survival in advanced stage ovarian cancer is an unmet need. Combining novel agents with NACT with a pharmacodynamic and a pharmacokinetic endpoint could lead to combinations that could

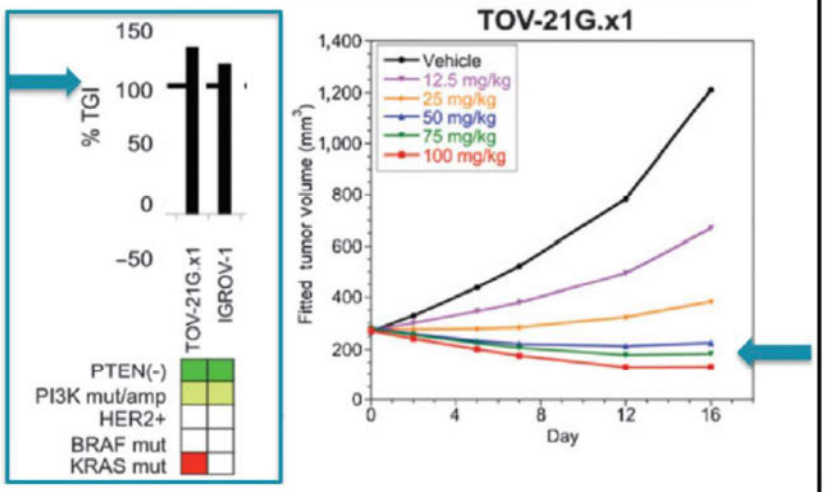

Figure 1. Single agent ipatasertib led to net tumor regression in 2 ovarian cancer xenograft models. (Lin et al. CCR 2013)

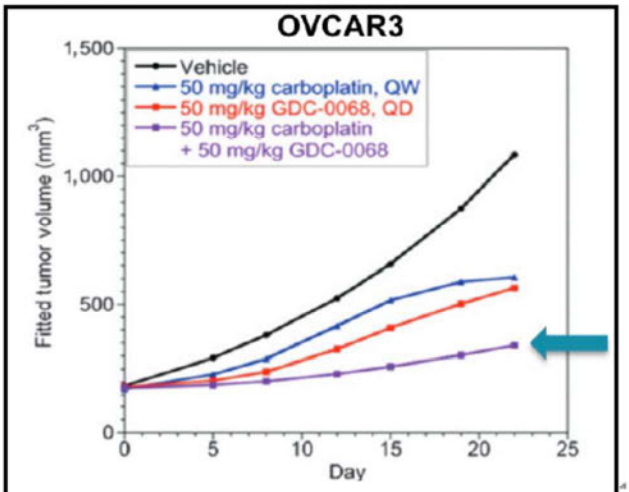

Figure 2. Combination carboplatin and ipatasertib led to decrease tumor volume compared to carboplatin alone. (Lin et al. CCR 2013)

improve response in future studies. Therefore, the patient population receiving NACT was chosen given it provides an opportunity for tissue collection and identifying pharmacodynamic changes. This may impact future trials and practice by utilizing pharmacodynamic changes to identify who may respond to ipatasertib. Up to 80% of ovarian cancers have alterations in the PIK3CA/AKT/PTEN pathway (Cancer Genome Atlas Research, 2011). Targeting AKT in cancer is a central node in the PI3K-AKT-mTOR signaling pathway in cancer. Additionally, AKT inhibition is less toxic than PI3K inhibitors, blocks mTOR, and avoids AKT activation caused by mTOR inhibitors. The AKT pathway controls multiple survival, metabolic, and growth promoting pathways.

Ipatasertib is an ATP-competitive AKT inhibitor that targets AKT1, 2, and 3. Cmax occurs at 0.5 to 3 hours after dose. This agent has a long half-life of ~48 hours with a steady state by day 8 of daily dosing. There have been no tissue PK studies thus far.

The activity of ipatasertib in preclinical models is demonstrated by the broad range of human cancer types and is enhanced by PTEN loss and PI3K mutants (Lin *et. al.*, 2013). Activity in ovarian cancer has been demonstrated as a single agent in 2 ovarian cancer xenograft models by net tumor regression (Figure 1). Both of these cell lines had PTEN loss and alterations in PI3K.

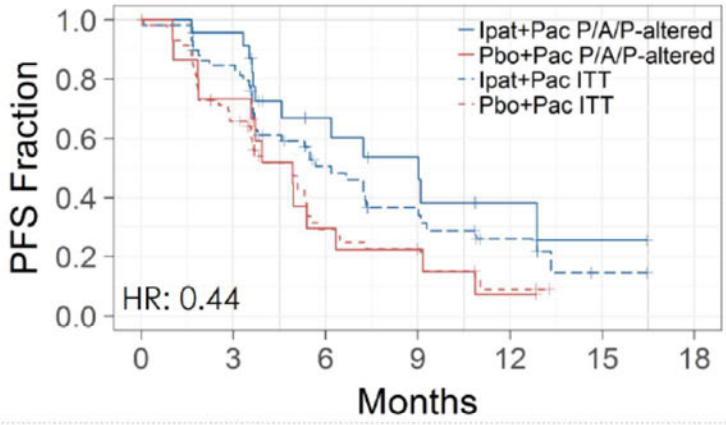

Figure 3. Metastatic TNBC tumors with PIK3CA/AKT/PTEN alterations in the Phase II multicenter, randomized paclitaxel +/- ipatasertib responded better than the ITT (intention to treat) unselected tumors (Kim et al. Lancet Oncology 2017)

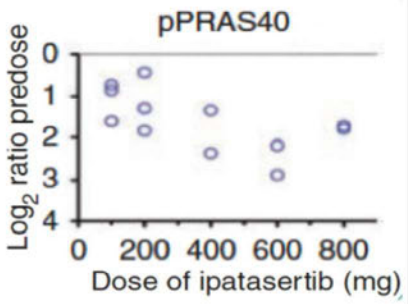

Figure 4. pPRAS40 tumor expression decreases in a dose-dependent fashion (Saura et al. Cancer Discovery 2017)

Additionally, ipatasertib has been shown to improve response to paclitaxel or carboplatin as seen in 3 xenograft models (breast, prostate, and ovarian cancer). In the ovarian cancer xenograft models, ipatasertib and carboplatin suppressed tumor growth compared to carboplatin vs. ipatasertib alone vs. vehicle alone[3] (Figure 2) (Lin *et. al.*, 2013). Furthermore, a multicenter, randomized Phase II trial on paclitaxel 80mg/m2 D1, 8, 15 +/- ipatasertib at 400mg daily 21 days on/7 days off q28 days in metastatic triple negative breast cancer showed an improvement in PFS in the tumors with PIK3CA/AKT/PTEN alterations when compared to the intention to treat that did not select altered tumors (Figure 3) (Kim *et. al.*, 2017). In terms of mechanistic biomarkers reflecting AKT inhibition, pPRAS40 is directly downstream of AKT.

A published Phase I trial in ipatasertib 600mg daily in solid tumors demonstrated a decrease in pPRAS40 in a dose-dependent fashion comparing tumor expression of the pre vs. on-treatment tumor (Figure 4) (Saura *et. al.*, 2017). Additional AKT pathway targets

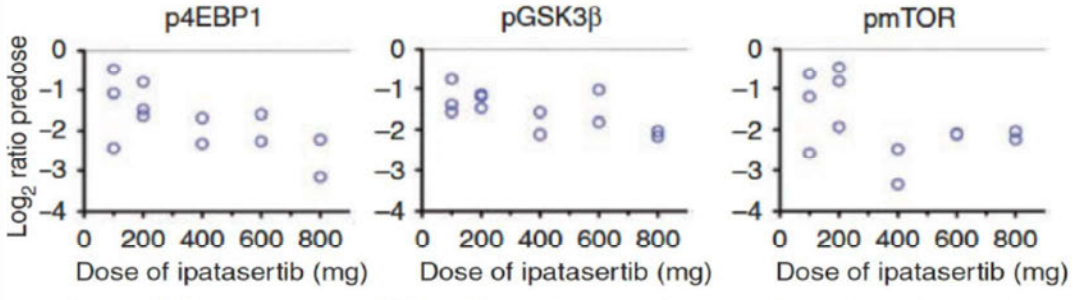

Figure 5. Downstream pAKT pathway targets decrease in a dose-dependent fashion comparing on-treatment to baseline. Saura et al. Cancer Discovery 2017)

(p4EPB1, pGSK3B, pmTOR) were found to be downregulated by ipatasertib in a dose-dependent fashion (Figure 5) when comparing pre- to on-treatment tumor biopsies. We propose a Phase I/IB trial of ipatasertib in combination with paclitaxel and carboplatin in newly diagnosed ovarian cancer given the high percentage of alterations in PIK3CA/AKT/PTEN alterations.

Pharmacodynamic and pharmacokinetic endpoints will be evaluated with baseline and post-ipatasertib tissue samples.

We have completed the dose escalation. There have been 12 participants enrolled and treated on DL1 (200mg) and DL2 (300mg). Among these 12 eligible and treated participants, 11 have been off study treatment.

Dose Level 1 had two cohorts with 7 patients enrolled and treated including 6 patients who were considered DLT-evaluable. Among these 6 DLT-evaluable patients, 1 had DLT based on treatment discontinuation > 14 days due to grade 3 maculo-papular rash.

For Dose Level 2, there were five patients in two cohorts with two DLTs. The DLTs were grade 2 diarrhea and grade 4 neutropenia. There was another participant during the postoperative period with a SAE for prolonged apneic arrest with anoxic injury. There were no delays in reaching surgical intervention in either DL1 or DL2. The MTD was determined to be 200mg daily. **(22-DEC-2023)**

Primary objectives and study design

The primary study objectives are to estimate the MTD in dose escalation phase and to evaluate the feasibility in expansion phase after the MTD is established for ipatasertib in combination with paclitaxel and carboplatin as neoadjuvant chemotherapy for ovarian cancer. This study consists of two phases with a sample size ranging from 21 to 36 patients: a dose-escalation phase for estimation of the MTD (PART I) and expansion phase (PART II).

Secondary objective

Objective response rate by RECIST 1.1 prior to IDS will be evaluated as a secondary endpoint. This is supported by a post-hoc exploratory analysis of ICON8, a randomized Phase 3 clinical trial. Of the 564 women who had RECIST-evaluable disease at trial entry, 348 (62%) had a RECIST complete or partial response following neoadjuvant chemotherapy. 73 (42%) of the 172 women with RECIST stable disease following neoadjuvant chemotherapy had complete cytoreduction. Of the RECIST complete or partial responses, 187 (56%) of the 335 women had a complete cytoreduction (reviewed in Morgan et al., 2021).

Ipatasertib

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of

the serine/threonine kinase Akt (protein kinase B) intended for oral administration (PO) (Investigator's Brochure, 2018). Ipatasertib selectively binds to the active conformation of Akt and inhibits its kinase activity (Lin et al., 2012). Ipatasertib is being developed for the treatment of cancers in which activation of the phosphatidylinositol 3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathway may be relevant for tumor growth or therapeutic resistance.

The serine/threonine kinase Akt is encoded by three closely related genes in mammals, AKT1, AKT2, and AKT3 (Investigator's Brochure, 2018). Akt is the central node of the PI3K-Akt-mTOR pathway, in which activation is associated with proliferation, cell cycle progression, and survival. The direct product of PI3K activity, the lipid second messenger, phosphatidylinositol (3,4,5)-trisphosphate (PIP3), promotes membrane association of Akt. Akt is phosphorylated at two critical residues for its full activation: a threonine residue in the activation loop of the kinase domain (threonine 308 in Akt1) by phosphoinositide-dependent kinase 1 (PDK1) and a serine residue within the hydrophobic motif of the regulatory domain (serine 473 in Akt1) by mTOR complex (mTORC) 2 (reviewed in Bhaskar and Hay, 2007). In turn, activated Akt phosphorylates and regulates the functions of numerous cellular proteins, including FOXO, mTORC1, and S6 kinase (reviewed in Manning et al., 2007).

The PI3K-Akt-mTOR pathway is activated by numerous genetic and non-genetic mechanisms across the spectrum of cancer (LoRusso, 2016). The most commonly found alterations in this pathway result from decreased expression or inactivating mutations of PTEN, a phospholipid phosphatase, activating and transforming mutations of PI3Kα, deregulation of receptor tyrosine kinase signaling, and amplification or activating mutations of receptor tyrosine kinases. In addition, alterations in Akt itself, including amplification and overexpression of individual Akt isoforms, as well as activating mutations in Akt, most commonly an E17K mutation in the pleckstrin homology (PH) domain of AKT1 that results in PI3K-independent membrane recruitment of Akt1, have been identified in a subset of human cancers (reviewed in Bellacosa et al., 2005; Brugge et al., 2007; Tokunaga et al., 2008).

Hyperactivation of Akt also occurs via deregulated signaling of many cell surface receptors and intracellular linkers and signaling molecules, and amplification/mutation of the epidermal growth factor receptor/ErbB growth factor receptor family members (reviewed in Brugge et al., 2007). Moreover, Akt activation has been associated with resistance to both chemotherapeutic agents and targeted agents such as trastuzumab and tamoxifen (Clark et al., 2002; Tokinaga et al., 2008).

Beside being an important driver of cell proliferation, growth, and survival, all of which are involved in tumorigenesis, Akt also plays a key role in glucose homeostasis and mediates the metabolic effects of insulin downstream of the insulin receptor (a receptor tyrosine kinase) (Whiteman et al., 2002; Dummler et al., 2007; Sale et al., 2008).

In summary, Akt is a central node in cell signaling downstream of growth factors, cytokines, and other cellular stimuli that play an important role in cancer development,

progression, and therapeutic resistance and is activated in most, if not all, human cancers (Deborah et al., 2005). The ubiquity and importance of Akt activation in human cancers provide a strong rationale for the development of therapeutics targeting Akt.

Mechanism of Action

Ipatasertib selectively binds to the active conformation of Akt and inhibits its kinase activity (Lin et al., 2012). Consistent with its mechanism of action in nonclinical studies, ipatasertib has proven to be especially effective on cells with activated Akt, including PTEN-null and PI3K-mutated tumor models, leading to suppression of the phosphorylation of its direct substrates. Consistent with the role of Akt in insulin signaling, ipatasertib also exhibited dose-dependent and reversible elevation of serum glucose in nonclinical studies. In vivo activity studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumors (Lin et al., 2013).

Nonclinical Studies

Extensive in vitro and in vivo pharmacology studies were performed to characterize the inhibitory potency and selectivity of ipatasertib for Akt isoforms and the effects of ipatasertib on cell proliferation, cell cycle progression, and apoptosis (Investigator's Brochure, 2018). In vivo activity was assessed in immunocompromised mice with human tumor xenografts representing multiple tumor types that are driven by PI3K-Akt pathway activation, including prostate cancer and breast cancer. In addition, in vitro and in vivo studies of ipatasertib combined with standard chemotherapeutic agents or anti-hormonal agents were carried out. Combination studies were also carried out with ipatasertib and an anti-programmed death-ligand 1 (PD-L1) antibody in a syngeneic murine breast tumor model, with or without paclitaxel. The results of these in vitro and in vivo pharmacology studies support the use of ipatasertib as a single agent or in combination with chemotherapeutic or targeted agents, including the anti-androgen agents abiraterone and enzalutamide, as well as an anti-PD-L1 antibody, for the treatment of patients with advanced or metastatic solid tumors.

In Vitro Studies

Ipatasertib is equipotent against all three Akt isoforms, with potencies ranging from 4 to 18 nM (Investigator's Brochure, 2018). Protein kinase A is a closely related AGC kinase family member, particularly with respect to the ATP-binding pocket. Ipatasertib was >100-fold less active at inhibiting the closely related kinase, protein kinase A. Representative IC50 values are as follows: 4 nM for Akt1, 18 nM for Akt2, 8 nM for Akt3, and 1,969 nM for protein kinase A. The IC50 values of the N-dealkylated metabolite of ipatasertib, M1 (G-037720) are as follows: 11 nM for Akt1, 106 nM for Akt2, and 69 nM for Akt3.

No significant off-target responses (≥50% inhibition or stimulation) were observed in in vitro biochemical binding assays that evaluated ipatasertib binding at 10 mcM against a

total of 66 pharmacologically significant receptors, ion channels, and transporters (Investigator's Brochure, 2018). When tested at 1 mcM, ipatasertib is selective for the Akt kinases over a panel of 230 kinases. With the exception of PKG1 (relative to which ipatasertib is >5-fold more selective for Akt1), ipatasertib displays a >60-fold selectivity for Akt1 over the next most potently inhibited non-Akt kinase in the panel. None of the toxicities observed in the repeat-dose studies were attributable to off-target kinase activity.

Ipatasertib potently inhibits phosphorylation of the proximal Akt substrate PRAS40, and this activity correlates with the anti-proliferative properties of this compound in a cell line dependent on the Akt pathway for growth and survival (Investigator's Brochure, 2018). Ipatasertib has demonstrated robust efficacy in nonclinical tumor models in which the PI3K-Akt pathway is activated through decreased expression of the PTEN tumor suppressor or mutational activation of the p110α catalytic subunit of PI3K (PIK3CA), including breast cancer models (Lin et al., 2013). Treatment of PC-3, MCF-7-neo/HER2, and BT474M1 cells with ipatasertib resulted in a dose-dependent block of cell cycle progression at the G1 phase. Ipatasertib treatment also caused a dose- and time-dependent increase in apoptotic and necrotic populations of MCF-7-neo/HER2 and BT474M1 cells (Investigator's Brochure, 2018). Collectively, these effects contributed to a dose-dependent inhibition of overall cell viability in response to ipatasertib treatment.

In addition to single-agent activity, the effect of ipatasertib was also evaluated in combination with chemotherapeutic agents. Combination effects were evaluated using both the Bliss independence model and the highest single agent (HSA) model (Lehár et al., 2007). Synergistic effects were seen in the androgen-independent prostate cancer cell line PC3M-LN4 when ipatasertib was combined with docetaxel. Neither agent alone was effective at inhibiting the viability of this cell line, with maximum inhibition of 37% and 27% observed at the highest concentrations of ipatasertib (20 mcM) and docetaxel (1 mcM) tested, respectively. Combination of the two agents resulted in increased inhibition of cell viability observed at lower concentrations of both ipatasertib and docetaxel, and maximum inhibition increased to 83%. Positive Bliss scores were observed at ipatasertib concentrations of 0.74-20 mcM in combination with all docetaxel concentrations tested (0.00098-1 mcM), and positive HSA scores were observed at ipatasertib concentrations of 0.25-20 mcM in combination with all docetaxel concentrations tested. Similar positive combination effects were observed in several other cancer cell lines, as well as with other chemotherapeutic agents such as 5-fluorouracil (5-FU) and cisplatin (Investigator's Brochure, 2018).

In Vivo Studies

In vivo efficacy of ipatasertib was established using various in vivo mouse xenograft models, in which the PI3K-Akt-mTOR pathway is aberrantly activated as a result of PI3Kα mutation or decreased PTEN expression (Investigator's Brochure, 2018). Anti-tumor activity was evaluated, shown as percentage of tumor growth inhibition (TGI) relative to vehicle controls for ipatasertib as a single agent or in combination with either

chemotherapeutics or targeted agents (e.g., docetaxel, paclitaxel, mFOLFOX6, abiraterone, and MDV3100). These in vivo studies demonstrated that ipatasertib has robust anti-tumor activity as a single agent and improved efficacy when administered in combination with other marketed or experimental cancer agents. All dose levels and combinations in the summarized efficacy studies were tolerated based on <20% body weight loss.

A pharmacodynamic (PD) and pharmacokinetic (PK) study was performed in nude mice bearing subcutaneous PC3-NCI prostate tumors to correlate plasma drug levels of ipatasertib with PD changes in the tumors (Investigator's Brochure, 2018). Following administration of a single oral dose of ipatasertib, plasma and tumor samples were collected between 1 and 24 hours for PK and PD analysis, respectively. Robust Akt pathway inhibition with ipatasertib was determined in vitro on the basis of the suppression of phosphorylated PRAS40 (pPRAS40) and phosphorylated S6RP (pS6RP) in PC3-NCI prostate tumor cells. Therefore, these PD markers relative to their total protein levels were also evaluated in vivo after mice bearing PC3-NCI prostate tumors were treated with ipatasertib. The chosen dose levels for ipatasertib reflected a subefficacious dose (12.5 mg/kg), a minimum efficacious dose (MED) (25 mg/kg), and a maximum efficacious dose (MaxED) (100 mg/kg) when administered daily in the PC3-NCI prostate model (Investigator's Brochure, 2018). Within 3 hours after drug administration, there was a dose-dependent decrease in the ratio of pPRAS40 to total PRAS40 (tPRAS40) compared with vehicle controls. The greatest modulation in PD response was achieved at 100 mg/kg of ipatasertib, with a >95% reduction in the ratio of pPRAS40 to tPRAS40 within 3 hours after dosing. At 8 hours post-dose, plasma levels of ipatasertib >2.6 mcM were achieved with 100 mg/kg, and this result correlated with a significant PD effect on the ratio of pPRAS40 to tPRAS40 ($p<0.001$) and, to a lesser extent, on the ratio of pS6RP to total S6RP (tS6RP) in PC3-NCI prostate tumors. These data demonstrate that inhibition of the Akt pathway in PC3-NCI prostate tumors for at least 8 hours correlates with maximum in vivo efficacy of ipatasertib.

Akt activation is associated with intrinsic and acquired resistance to chemotherapy (Clark et al., 2002; Tokunaga et al., 2008). In vivo studies of ipatasertib combined with standard chemotherapeutic agents were carried out in multiple models (Investigator's Brochure, 2018). In the HCI-001 TNBC xenograft model, the combination of docetaxel and ipatasertib enhanced TGI (89% for the combination) compared with either single agent alone (64% and 63%, respectively). In the MCF-7 breast tumor xenograft model, the combination of paclitaxel and ipatasertib enhanced TGI (97% for the combination) compared with either single agent alone (83% and 42%, respectively). Additionally, in the STO#240 primary gastric tumor xenograft model, the combination of ipatasertib and mFOLFOX6 enhanced TGI (90%) compared with either single agent alone (55% and 54%, respectively) (Investigator's Brochure, 2018). All combinations were well tolerated, with no added body weight loss compared with docetaxel, mFOLFOX6, or paclitaxel alone.

A combination study between ipatasertib, paclitaxel, and anti-PD-L1 was also carried out in the EMT6 syngeneic breast tumor model (Investigator's Brochure, 2018). The

combination of paclitaxel, ipatasertib, and anti-PD-L1 showed no antagonism either as a triple combination or double combination between any two agents, with a 89% TGI observed for the triple combination compared with each single agent alone (27%, 22%, and 66%, respectively). All combinations were well tolerated. To test the hypothesis of androgen receptor and PI3K-Akt-mTOR pathway crosstalk and reciprocal feedback activation, in vivo studies of ipatasertib combined with either the androgen biosynthesis inhibitor abiraterone or the androgen receptor antagonist enzalutamide (MDV3100) were conducted in the LuCaP35V primary prostate cancer model (Investigator's Brochure, 2018). The combination of abiraterone and ipatasertib greatly enhanced TGI (57% for the combination) compared with either single agent alone (25% and 17%, respectively). Additionally, the combination of enzalutamide and ipatasertib greatly enhanced TGI (96% for the combination) compared with either single agent alone (46% and 57%, respectively). In all studies, the treatment combinations were well tolerated.

Safety Pharmacology

The 23 mcM IC50 value for in vitro cardiac hERG channel inhibition is approximately 38-fold greater than the steady-state unbound concentration of ipatasertib in patients administered the proposed clinical dose of 400 mg QD (280 ng/mL, 0.61 mcM) and is approximately 23-fold greater than the steady-state unbound concentration of ipatasertib in patients administered the MTD dose of 600 mg QD (463 ng/mL, 0.99 mcM)(Investigator's Brochure, 2018). In addition, no ipatasertib-related effects on cardiovascular or respiratory parameters were observed in monkeys following ipatasertib administration at doses of up to 30 mg/kg in a dedicated Good Laboratory Practice (GLP), cardiovascular, safety pharmacology study, or in GLP repeat-dose toxicity studies of up to 26-week duration.

Overview of Clinical Development

There are currently no FDA approved AKT inhibitors for cancer treatment. Ipatasertib is currently under investigation in phase 1, 2, and 3 clinical trials in castration resistant prostate cancer and metastatic breast cancer. In a three-stage study, 30 patients were enrolled in the dose-escalation (stage I) and 22 patients in the two dose expansion cohorts (11 metastatic breast cancer and 5 patients with metastatic castration-resistant prostate cancer; stage II), or all solid tumors (n=6, stage III) (Saura et al, 2017). The most common cancers were breast cancer (n=16) or colorectal cancer (n=14), with a median of six prior lines of therapy (range, 1-17). Oral ipatasertib was administered daily for 21 days followed by 7 days off (21/7 day dosing schedule) every 28 days with doses ranging from 25-800 mg. Dose limiting toxicities (DLTs) at 800 mg were asthenia and nausea. The maximum tolerated dose for ipatasertib was 600 mg daily on a 21-day on/7-day off schedule which was used for the expansion cohorts in stage II and stage III. Although the MTD was 600mg daily, the recommended dose for further development is 400 mg daily based upon overall tolerability profile. Furthermore, a Phase Ib/II trial of ipatasertib 200mg vs 400mg daily dosing in combination with abiraterone 1000mg and prednisone/prednisolone 5mg twice daily was completed (deBono et al., 2018). This study demonstrated that the most common AEs leading to discontinuation in the

ipatasertib 400mg arm were diarrhea (2/84 = 2.4%) and hyperglycemia (2/84 = 2.4%). AEs that led to discontinuation occurred in 10 (11.9%) and 7 (8%) patients in the ipatasertib 400mg and 200mg cohort respectively. There were no deaths related to study treatment thus supporting 400mg daily dosing.

In 51 treated patients in the single agent study, the most common causally-related grade 2 or greater adverse events across all dose levels were as follows: diarrhea (35%), nausea (27%), asthenia (25%), hyperglycemia (10%), decreased appetite 6%, rash (6%), and vomiting (6%). Grade 3 events were diarrhea (n=4), asthenia (n=3), hypercholesterolemia (n-1), hyperglycemia (n=1), hypophosphatemia (n=1), nausea (n=1), and toxic skin eruption (n=1). No grade 4 events were observed. Timing to the first onset of diarrhea, nausea, fatigue, and rash typically occurred during cycle 1. As proof of mechanism, reduction in the substrates pGSK3β and pPRAS40 was demonstrated in platelet-rich plasma. In terms of exposure, ipatasertib ≥ 400 mg was associated with pGSK3β reduction ≥ 80%, and even at doses < 100 mg greater than 50% inhibition was observed. In addition, comparing pretreatment and on-treatment tumor biopsies, there was a reduction in pRAS40, pEBP1, pS6, and pmTOR in a dose-dependent manner, as measured by reverse phase protein array.

There is clinical evidence of anti-cancer activity with ipatasertib. Across all dosing cohorts, 16 of 47 patients (34%) had stable disease (SD) or incomplete response, per RECIST criteria, and 6 patients had a progression free survival (PFS) >6 months (18% in those who received 400 mg or 600 mg). Of the 41 patients with known molecular status, SD was observed in 6/9 patients with PTEN loss, PIK3CA, or AKT mutations in their tumor, as compared to 3/9 who had progression. Those with a PIK3CA mutation (n=6) or AKT mutation (n=1) remained on study longer with ipatasertib compared to those without these mutations (n=33); median treatment time was 84 vs. 63 days.

Notably, the one patient with an AKT1 mutation (E17K) had a HER2- negative metastatic breast cancer that had progressed on liposomal doxorubicin, cyclophosphamide, and most recently capecitabine (on drug for ~90 days); while on ipatasertib her CA15-3 declined by >50% and she remained on study for 235 days (confidential: Genentech). These data suggest that AKT inhibition with ipatasertib may provide a novel therapeutic approach and serve as the rationale for investigating this agent in patients with AKT mutated tumors.

LCM-RPPA-based pAKT S473 and T308 as Exploratory Biomarkers for Ipatisertib Response Prediction

Despite extensive genomic and transcriptomic profiling, it remains unknown how signaling pathways are differentially activated and how tumors are differentially sensitized to certain perturbations. Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer with poor prognosis and high recurrence and metastasis rate, highlighting the need for more effective therapeutic approaches with appropriate diagnostic biomarkers. Due to the molecular heterogeneity of TNBC, a key aspect for targeted therapy is identifying tumors that are most likely to be sensitive to the specific oncogenic signaling perturbation to maximize the clinical benefit.

In our recently published study with Genentech, we aimed to characterize AKT signaling activity and its association with other genomic or IHC-based PI3K/AKT pathway biomarkers as well as the clinical activity of ipatasertib (AKT inhibitor) in the FAIRLANE trial. 151 patients with early triple-negative breast cancer (TNBC) were randomized 1:1 to receive paclitaxel with ipatasertib or placebo for 12 weeks prior to surgery. We used a laser capture microdissection (LCM) reverse-phase protein microarray (RPPA) based workflow to examine the total level and/or phosphorylation states of over 100 proteins including the quantitative activation levels of AKT, the direct drug target of ipatisertib, as well as other members of the PI3K/AKT and mTOR signaling pathway as well in the isolated tumor epithelium.

One hundred and twenty-five baseline/pre-treatment tumors were analyzed. Our recently published results showed that of all genomic and protein/phosphoprotein biomarkers considered only baseline pAKT S473 and T308 levels predicted for benefit of ipatasertib in TNBC. Importantly, tumors with high pAKT S473 and T308 levels exhibited association with enriched ipatasertib activity regardless of genomic PIK3CA/AKT/PTEN status. This study provides proof-of-concept that the baseline phosphorylation levels of AKT, the direct target of ipatasertib, could have predictive value and may possess an improved means of biomarker-based patient selection for AKT inhibitors and diagnostic utility for precision medicine. **(24-APR-2023)**

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).

Submission of tissue is **required.** Investigators should check with their pathology department regarding release of tissue before approaching patients about participation in the trial (see Sections 3.1.4, 4.1, and 10 for details).

3.1 Eligibility Criteria

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

3.1.1 Pathologically proven diagnosis of ovarian cancer (Ovarian cancer = fallopian tube cancer, ovarian cancer, primary peritoneal cancer). Required data element: submission of pathology report.
Patients with the following histologic cell types are eligible:
a. High grade serous
b. Endometrioid adenocarcinoma, grade 3

Genomic/genetic testing results will be a data collection element if performed as part of usual care (Germline genetic testing, tumor genomic testing, HRD testing).
Genetic/genomic testing results should be uploaded if they become available anytime

during conduct of the study.

3.1.2 Appropriate stage for study entry defined as Stage III or Stage IV based on the following diagnostic workup:
a. History/physical examination within 14 days prior to registration
b. Imaging with CT C/A/P within 28 days prior to registration;
Please see protocol-specific assessment requirements in section 4.1 Pre-treatment Assessment Table.

3.1.3 Patients must have evaluable disease or measurable disease defined by RECIST v 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT or MRI. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.1.4 Pre-treatment formalin-fixed, paraffin-embedded (FFPE) tumor block collected from laparoscopy (preferred) or five 18G cores by radiology/interventional radiology (acceptable) must be available for submission.

3.1.5 Disease must be considered unresectable via primary debulking surgery and in need of neoadjuvant chemotherapy (NACT) prior to debulking surgery. This assessment of unresectability can be made via imaging or laparoscopic scoring.

3.1.6 No prior therapy directed at ovarian cancer.

3.1.7 Age ≥ 18 years

3.1.8 ECOG Performance Status ≤ 2 within 14 days prior to registration.

3.1.9 Adequate hematologic function within 14 days prior to registration defined as follows:
a. Absolute neutrophil count ≥ 1,000/mcl
b. Platelets ≥ 100,000/mcl
c. Hemoglobin ≥ 10g/dl **(07-AUG-2023)**

3.1.10 Adequate renal function within 14 days prior to registration defined as follows:
Creatinine ≤ institutional/laboratory upper limit of normal (ULN) or Creatinine clearance (CrCL) or estimated Glomerular filtration rate (eGFR) of ≥60 mL/min estimated using either the Cockcroft-Gault equation, the Modification of Diet in Renal Disease Study, or as reported in the comprehensive metabolic panel/basic metabolic panel (eGFR).

3.1.11 Adequate hepatic function within 14 days prior to registration defined as follows:
a. Total bilirubin ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
b. AST(SGOT)/ALT(SGPT) ≤ 3 x ULN

3.1.12 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. As clinically indicated, patients with a history of cardiac disease or history of cardiotoxic agents should have an echocardiogram or MUGA within 28 days of treatment showing an EF of ≥ 50%. **(07-AUG-2023)** (See Appendix III.)

3.1.13 Women of childbearing potential (WOCBP) must agree to use two forms of birth control (hormonal or barrier method of birth control; abstinence) agree to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 28 days after the last dose of ipatasertib and agreement to refrain from donating eggs during this same period.

3.1.14 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.

3.1.15 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.16 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.17 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.

3.1.18 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.

3.1.19 Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Ineligibility Criteria

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

3.2.1 Prior treatment with agent(s) targeting PI3K/AKT/mTor pathway.

3.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ipatasertib, paclitaxel or carboplatin.

3.2.3 Currently receiving any other investigational agents or has received an investigational agent within 4 weeks of study registration.

3.2.4 Abnormal gastrointestinal function. This includes GI obstruction or bleeding or signs/symptoms thereof within 3 months of study registration.

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

3.2.6 Received prior radiotherapy to any portion of the abdominal cavity or pelvis.

3.2.7 Patients with uncontrolled intercurrent illness.

3.2.8 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Patients with active infections requiring intravenous antibiotics.

3.2.10 Patients with diabetes either requiring insulin therapy or with a baseline fasting glucose ≥160 mg/dL and/or high HbA1c (>8), suggesting poorly controlled diabetes. Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours. (See protocol section 4.1for the definition of fasting).

3.2.11 Patients with Grade ≥ 2 uncontrolled or untreated hypercholesterolemia (>300 mg/dL) or hypertriglyceridemia (>300 mg/dL).

3.2.12 Known congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) > 470 milliseconds. **(07-AUG-2023)**

3.2.13 History of or active inflammatory bowel disease (e.g., Crohn's disease and/or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis).

3.2.14 Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia).

3.2.15 Patients with known brain metastases or leptomeningeal disease are not eligible, as prior treatment directed at ovarian cancer is not allowed.

3.2.16 Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to registration.
Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.
Please see Appendix IX for drug interactions handout.

3.2.17 Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis, current drug or alcohol abuse, or cirrhosis.

3.2.18 Pregnant women are excluded from this study because ipatasertib is an oral AKT inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ipatasertib, breastfeeding should be discontinued if the mother is treated with ipatasertib. These potential risks may also apply to other agents used in this study.

3.2.19 Inclusion of Women and Minorities

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

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

4.1 PRE-TREATMENT ASSESSMENTS

Cycle 1 Day 1 treatment should begin within 7 days of registration.

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days) (Cycle 1, Day 1)
History and Physical	≤ 14 days	≤ 14 days
Review concomitant medications *no strong CYP450 3A inhibitor or inducer within 2 weeks or 5 drug-elimination half-lives (whichever is longer) of first dose of ipatasertib	≤ 14 days	≤ 14 days
Vital Signs (Blood Pressure, Heart Rate, Temperature, Pulse Oxygen Saturation)	≤ 14 days	X
Height*	X	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, **fasting** glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT) NOTE: Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.	≤ 14 days	≤ 14 days
Hgb A1C	≤ 28 days	≤ 28 days
Lipid Panel (including Cholesterol, Triglycerides)	≤ 28 days	≤ 28 days
CA-125	≤ 28 days	≤ 28 days
Electrocardiogram (ECG)	≤ 3 months	≤ 3 months
Echocardiogram or MUGA if clinically indicated	≤ 28 days	≤ 28 days
Pregnancy test (for women of childbearing potential) Urine or serum testing is permitted	≤ 14 days	≤ 72 hours
Radiographic Tumor Measurement[1]	≤ 28 days	≤ 28 days
Biospecimen Submissions (see Section 10.4 for details)		
Formalin-fixed, paraffin-embedded (FFPE) tumor tissue block		Mandatory[2]
EDTA whole blood		Mandatory[2]
Frozen normal tissue and tumor		Optional[2]
Na Hep whole blood		Optional[2]

(07-AUG-2023)

1 Radiographic tumor measurements should be obtained via imaging of the chest (CT chest [preferred] or CXR), and CT of the abdomen and pelvis (MRI w/contrast may be substituted for CT w/contrast in patients who cannot tolerate CT w/ contrast) 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). CT w/ contrast is the preferred modality. PET CT is NOT to be used for any disease assessment or reassessment unless there is documentation that PET/CT is of diagnostic quality equal to CT with contrast.

2 Biospecimens should not be shipped until after patient registration and Bank ID assignment.
* Height measurement is performed on adult participants during admission or at initial visit to an outpatient facility per clinical practice. As height measurement on adults is not routinely performed during follow up visits, the height measurement previously recorded for adult participants may be used for calculating drug dosages or body surface area as applicable and can be used for baseline and follow up visits data capture.

4.2 ASSESSMENTS DURING TREATMENT

Assessments	Prior to Day 1 of each cycle	Timed (Treatment Cycle Independent)
History and Physical	≤ 3 days	
Concomitant Medications	≤ 3 days	X – evaluate any new medications particularly CYP3A inhibitors or inducers started anytime while on ipatasertib
Vital Signs	X	
Weight	≤ 3 day	
Performance Status	≤ 3 days	
Toxicity Assessment	≤ 3 days	
CBC/Differential/Platelets	≤ 3 days	
Chemistries (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, **fasting** glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT) NOTE: Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.	≤ 3 days	
Lipid Panel (including Cholesterol, Triglycerides)	≤ 3 days	
CA125	≤ 3 days	
Radiographic Tumor Measurement		X[1]
Review of pill diary to assess treatment compliance	X	X
Repeat ECG		X- as clinically indicated
Biospecimen Submissions (see Section 10.4 for details)		
Formalin-fixed, paraffin-embedded (FFPE) tumor		Mandatory[2]

tissue block		
Frozen normal tissue and tumor		Mandatory[2]
Plasma		Mandatory[2]
Na Hep whole blood		Optional[2]

(07-AUG-2023)

1 **First assessment scan occurs at 3 weeks (+/- 7 days) post cycle 3 of neoadjuvant paclitaxel, carboplatin, and ipatasertib and prior to IDS.** Radiographic tumor measurements are obtained until disease progression is confirmed; at the investigator's discretion, they can be repeated any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. Utilize the **same** imaging modality of chest, abdomen, and pelvis (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT is NOT to be used for any disease assessment or reassessment.

2 Collected at interval debulking surgery (IDS).

4.3 ASSESSMENTS IN FOLLOW UP

Assessments	Timing
Post-operative chemotherapy	**Post-operative chemotherapy (e.g., paclitaxel/carboplatin or other) will be given as per usual care. Dates, drug names, and drug doses of post-operative chemotherapy will be collected.**
Vital Status	**90 days after last dose of ipatasertib (+/- 14 days)**
Toxicity Assessment	**Safety follow-up visits will be conducted at 30 days (+/- 7 days) after the last dose of ipatasertib and 90 days (+/- 14 days) after the last dose of ipatasertib.** These follow-ups may be conducted in person, via telemedicine, or via phone. Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For all adverse events that occur within 30 days of last protocol treatment please report on the Toxicity form for the last cycle of therapy administered. For reporting of delayed toxicity, see Section 7.
Radiographic tumor measurement	**Radiographic tumor measurement will be completed at 3 weeks (+/- 7 days) after 3 cycles of paclitaxel, carboplatin, ipatasertib and before IDS.**

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.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Protocol treatment should begin within 7 days of registration. Patients with newly diagnosed ovarian cancer, who have fulfilled the eligibility requirements according to Section 3, will receive neoadjuvant (NACT) chemotherapy of ipatasertib in combination with paclitaxel and carboplatin for 3 cycles (1 cycle = 21 days) followed by single-agent ipatasertib until 24 hours prior to interval debulking surgery. Ipatasertib will be administered according to the following dose escalation schema (Table 1).

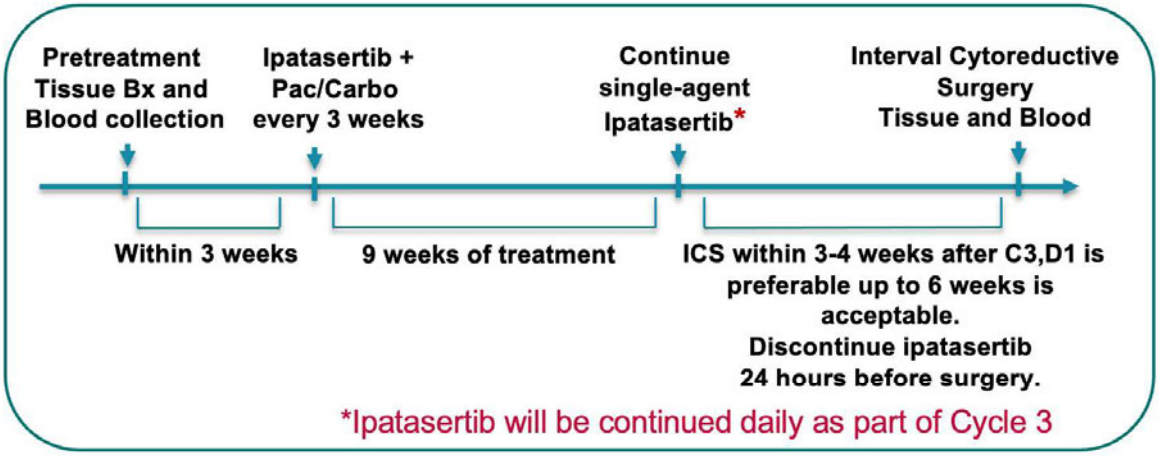

Table 1. Dose escalation schema

Dose Escalation Schedule			
Dose Level	**Dose***		
	Ipatasertib	***Paclitaxel***	***Carboplatin***
Level -1	100mg	175mg/m2	AUC 5
Level 1+	**200mg**	**175mg/m2**	**AUC 5**
Level 2	300mg	175mg/m2	AUC 5
Level 3	400mg	175mg/m2	AUC 5

+ The maximum tolerated dose of ipatasertib was determined to be dose level 1 200 mg. The trial is now only open to accrual for the expansion phase. **(22-DEC-2023)**

The dose of ipatasertib will begin at 200mg oral daily, continuously (one cycle = 21 days)

for 3 cycles taken concurrently with paclitaxel and carboplatin. The dose escalation scheme is DL1 at 200mg, DL2 at 300mg, and DL3 at 400mg with a de-escalation (DL-1) at dose level of 100mg. The dose escalation phase of this trial has concluded as of December 22, 2023.

Each dose of ipatasertib should be taken with a minimum of 3 ounces (90 mL) of fluid. Ipatasertib may be taken with or without food. If a dose is missed or omitted (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose the following day. Missed, omitted, or vomited doses will not be made up.

5.1 Agent-Based Therapy

See Appendix IV – Carboplatin Dose Calculation Instructions
See Appendix V – General Therapy Guidelines

Paclitaxel 175 mg/m^2 IV over 3 hours Day 1
Carboplatin AUC 5 IV over approximately 30-60 minutes Day 1
Paclitaxel and Carboplatin will be administered every 3 weeks for a total of 3 cycles.

5.1.1 Pre-medication for Paclitaxel

For all cycles where paclitaxel is to be administered, it is recommended that a preparative regimen be employed, to reduce the risk associated with hypersensitivity reactions. This regimen should include a standard dose of dexamethasone (either IV or PO), an antihistamine H1 (diphenhydramine 25-50 mg IV or orally, or an alternate H1blocker), and a standard dose of antihistamine H2 IV (such as famotidine). Paclitaxel preparative regimen can be altered at the discretion of the treating investigator.

Because of the risk of hyperglycemia with ipatasertib, it is recommended that dexamethasone doses be minimized to the extent that is clinically feasible.
For example, if Cycle 1 is tolerated without apparent hypersensitivity reaction, a reduction in dexamethasone premedication dose should be considered for subsequent cycles if permitted by institutional standard of care.

It is anticipated that nausea and vomiting may be a significant side effect of this regimen (due to carboplatin administration). An antiemetic regimen is suggested (per institutional, NCCN and/or ASCO guidelines). Antiemetic regimen can be altered at the discretion of the treating investigator.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Supportive/Ancillary Care and Concomitant Medications

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

Herbal and Nutritional Supplement
The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of 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.

Because there is a potential for interaction of ipatasertib 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 Principal Investigator 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. Appendix IX (Patient Drug Interactions Handout and Wallet Card) should be provided to patients.

5.3 Duration of Therapy

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

- Disease progression defined per RECIST 1.1,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- 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 re study consent withdrawal)
- See Section 6.1 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.

5.4 Definition of Dose-Limiting Toxicity (DLT)

Dose-limiting toxicities (DLTs) will be defined by drug related adverse effects that occur within the first cycle of neoadjuvant chemotherapy and include at least possibly related to any of the 3 drugs and meet the criteria below as evaluated by NCI CTCAE v.5 unless clearly unrelated to study therapy.

The definition of DLT include the following:

1. Inability to tolerate assigned ipatasertib dose for at least 16 of the planned 21 doses.

2. Grade ≥ 3 fasting hyperglycemia
3. Grade ≥ 2 ALT, AST, or total bilirubin elevation >2x ULN
4. Grade ≥ 2 colitis/enterocolitis
5. Grade ≥ 2 diarrhea – persistent despite medical management. Ipatasertib-related diarrhea could be prevented with a prophylactic dose of loperamide 2 mg every 4 hours. Duration of diarrhea can be minimized by taking ipatasertib with food.
6. Grade ≥ 3 rash – persistent despite medical management.
7. Grade ≥ 2 pneumonitis
8. Neutropenic fever
9. Any ≥ Grade 3 non-hematologic toxicity (exceptions may include Grade 3+ amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis; Grade ≥ 3 asymptomatic electrolyte abnormality that lasts <72 hours)
10. Grade 3+ fatigue ≥ 1 week
11. Grade ≥ 3 nausea/vomiting for >72 hours despite adequate antiemetic and other supportive care
12. Grade ≥ 2 diarrhea – persistent for > 72 hours despite medical management
13. For patients with hepatic metastases, AST or ALT >8xULN or AST or ALT >5x ULN for >=14 days
14. Any death not clearly due to the underlying disease or extraneous causes

5.5 Treatment and Dose Escalation Plan for Dose Escalation Phase

The dose escalation phase indicated Dose Level 1 as the MTD. Based on the safety data review by the study team and CTEP, patients enrolled to the expansion phase will be treated at Dose Level 1 (See Section 5 Table 1) **(22-DEC-2023)**

Dose escalation decisions and the maximum tolerated dose will be defined based on DLTs that occur **within the first cycle of neoadjuvant chemotherapy**.

A standard 3+3 with dose de-escalation design will be used to determine the MTD of ipatasertib in combination with paclitaxel and carboplatin in dose escalation phase. Patients will be accrued in cohorts of size 3. The dose level combinations and orders are presented in Table 1.

The starting dose level (Dose Level 1, DL1) will consist of paclitaxel 175mg/m^2, carboplatin (AUC 5), every 21 days, and ipatasertib at 200 mg po daily.

Three patients will be enrolled at Dose Level 1 (DL1). Up to 3 patients will be enrolled and treated at the assigned dose level. If no DLTs are observed in the first 3 patients, then dose escalation may continue, and 3 new patients may be enrolled at the next dose level. If only one patient is observed with a DLT event in the first 3 patients, up to 3 additional patients will be enrolled and treated at the same dose level before dose escalation can proceed. If no further DLTs are observed, then dose escalation may continue. When two or more patients at a dose level have experienced a DLT, that dose level will be discontinued, and the previous dose level will be considered: if six patients have been treated at that dose level, it will be considered as the MTD; if three patients have been

treated at that dose level, up to three more will be treated at that dose level. For a dose level to be declared the MTD, a total of 6 patients must be treated at a dose level with no more than 1 patient experiencing a DLT. The details for the number of patients with observed DLTs and corresponding dose escalation decisions for each dose level are outlined as the following.

Dose Level 1 (DL1), 200 mg ipatasertib + paclitaxel + carboplatin		
Num. of patients treated at the current dose†	Num. of patients with DLTs	Action
3	0	Escalate to dose level 2
3	1	Add 3 more patients at current dose level
3	≥ 2	De-escalate to dose level -1
6	1	Escalate to dose level 2
6	≥ 2	De-escalate to dose level -1

Dose Level 2 (DL2), 300 mg ipatasertib + paclitaxel + carboplatin		
Num. of patients treated at the current dose†	Num. of patients with DLTs	Action
3	0	Escalate to dose level 3
3	1	Add 3 more patients at current dose level
3	≥ 2	Dose level 1 is MTD if max of 1/6 DLT on dose level 1*
6	1	Escalate to dose level 3
6	≥ 2	Dose level 1 is MTD if max of 1/6 DLT on dose level 1*

*If only 3 patients were enrolled on Dose Level 1, prior to escalation to DL2, another 3 patients will need to be enrolled on DL1.

Dose Level 3 (DL3), 400 mg ipatasertib + paclitaxel + carboplatin		
Num. of patients treated at the current dose†	Num. of patients with DLTs	Action
3	≤ 1	Add 3 more patients at current dose level
3	≥ 2	Dose level 2 is MTD if max of 1/6 DLT on dose level 2*
6	≤ 1	Dose level 3 declared as MTD
6	≥ 2	Dose level 2 is MTD if max of 1/6 DLT on dose level 2*

*If only 3 patients were enrolled on Dose Level 2, prior to escalation to DL3, another patients will need to be enrolled on DL2.

Dose Level -1 (DL-1), 100 mg ipatasertib + paclitaxel + carboplatin		
Num. of patients treated at the current dose†	Num. of patients with DLTs	Action

3	≤ 1	Add 3 more patients at current dose level (DL-1)
3	≥ 2	Discontinue the trial
6	≤ 1	Dose level -1 declared at MTD
6	≥ 2	Discontinue the trial

†Patients means they are eligible for this study and evaluable for DLTs.

No intra-patient dose escalations will be allowed.

No patient may be enrolled at the next higher dose level until all patients at the previous dose level have been followed through the end of the first cycle.

For DLT evaluation, a patient is treated as having completed the first cycle of neoadjuvant chemotherapy if this patient completes at least 80% of ipatasertib out the 21 daily ipatasertib doses.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **related** to ipatasertib toxicity of any grade will be considered a DLT by the definition in 5.4.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **unrelated** to ipatasertib toxicity of any grade will be considered for replacement after discussion with CTEP. The reason for not completing the cycle needs to be determined and well annotated.

DLTs and other toxicities are discussed among the study chairs, the phase I committee chair, the study statistician and the site investigators. The discussions are the basis for the decisions regarding dose escalation according to the rules of the protocol. These discussions will occur at regularly scheduled conference calls. See section 5.4 for dose-limiting toxicity definitions.

Safety data will be reviewed with CTEP prior to opening expansion phase.

5.6 Treatment Plan for Expansion Phase

Once the MTD is determined from the dose-escalation phase, that dose will be used for the expansion phase unless clinical judgement indicates that a lower dose be used. DLTs will be based the first 21-day cycle.

For DLT evaluation, a patient is treated as having completed the first cycle of neoadjuvant chemotherapy if this patient only misses 4 doses or less of ipatasertib out of the 21 daily ipatasertib doses.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **related** to ipatasertib toxicity of any grade will be considered a DLT by the definition in 5.4.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **unrelated** to ipatasertib toxicity of any grade will be considered for replacement after discussion with CTEP. The reason for not completing the cycle needs to be determined and well annotated.

Safety data will be reviewed with CTEP prior to opening expansion phase. The design of the expansion phase is described in Section 13.4.

The dose escalation phase indicated Dose Level 1 as the maximum tolerated dose (MTD). Based on the safety data review by the study team and CTEP, patients enrolled to the expansion phase will be treated at Dose Level 1 (See Section 5 Table 1) **(22-DEC-2023).**

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 General Guidelines

Dose modifications for paclitaxel and carboplatin chemotherapy will be performed according to standard practice of institutional guidelines; details in this section can be used as a guidance. Reasons for dose modifications or delays, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF.

General guidelines for dosage/schedule modification can be summarized as follows:

- For toxicities assessed by the investigator to be unlikely to develop into serious or life-threatening events, treatment may be continued at the same dose without reduction or interruption.
- If any observed toxicity is attributable to only one drug as assessed by the investigator, the dose of the other drug(s) may not require modification.
- Patients who require chemotherapy dose reductions and tolerate the reduced dose for more than one cycle (28 days) may be allowed to increase back to a 100% dose at the treating physician's discretion.
- Chemotherapy may be delayed to manage toxicity. Delays up to 4 weeks (approximately 28 days) are permitted. Any delay longer than 4 weeks for an adverse event will require permanent discontinuation of paclitaxel and carboplatin treatment, but the patient may continue the ipatasertib, after discussion with the Medical Monitor.

6.2 Stopping Criteria

The criteria to stop the study will be if 3 or more patients are unable to proceed with their debulking surgery (due to unresolved toxicities precluding the ability to have surgery) or if there is an unreasonable delay in the ability to complete debulking surgery due to excessive toxicity.

6.3 Ipatasertib Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events

Ipatasertib can be taken with or without food. If a dose is missed or omitted (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose the following day. Missed, omitted, or vomited doses will not be made up.

In general, patients should be closely monitored for GI effects and patients experiencing nausea, vomiting, stomatitis/oral mucositis, or diarrhea are to be treated and managed per standard of care and per protocol guidelines, including hydration if clinically indicated to prevent renal insufficiency due to fluid depletion. If the GI effects are attributable to ipatasertib as assessed by the investigator, the ipatasertib dose may be interrupted or reduced. Patients whose GI symptoms cannot be adequately managed should discontinue ipatasertib.

Fasting glucose levels should be carefully monitored per protocol guidelines. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision. Hyperglycemia should be managed per institutional standards of care, and per protocol guidelines. Use of oral anti-hyperglycemic agents (e.g., metformin) for patients experiencing Grade ≥2 hyperglycemia should be considered. For Grade ≥3 hyperglycemia, ipatasertib dosing may be interrupted or reduced per protocol guidelines. Endocrinology consultation should be considered for management of hyperglycemia, especially prior to use of insulin for asymptomatic hyperglycemia (due to the risk of hypoglycemia).

Treatment-related rash, including cases of Grade 3 and Grade 4 rash, has occurred in patients receiving ipatasertib treatment. In general, the rash commonly manifested as a maculopapular type with or without pruritus. Most of the observed Grade 3 rashes occurred approximately 1-3 weeks after the first dose of ipatasertib. In most of the cases with Grade 3 rash requiring dose interruption, ipatasertib dosing was resumed with dose reduction without recurrence of rash. Rash and other dermatologic events should be closely monitored and managed per standard of care and protocol guidelines. In general, for severe rash, dosing of ipatasertib should be held and patients should be treated with supportive therapy per standard of care; use of topical antihistamines as well as topical or systemic corticosteroids should be considered.

Dosage Modification for Ipatasertib

If the patient does not tolerate the QD dosing of the ipatasertib, dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea. No more than two dose reductions of ipatasertib per patient (Dose re-escalation is not permitted for ipatasertib). Given the MTD is at DL1 of 200mg daily and per the dose-expansion, there will only one dose level reduction to 100mg daily. **(22-DEC-2023)**

Treatment Interruption

Ipatasertib treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. If ipatasertib has been withheld for >2 weeks because of treatment-related toxicity, the patient should be discontinued from ipatasertib. Ipatasertib treatment may be suspended for reasons other than toxicity (e.g., surgical procedures). Any hold for toxicity should be considered a DLT. If there is a length of time longer than 2 weeks or concomitant requirement to modify primary chemotherapy, this should result in discontinuation of ipatasertib.

Ipatasertib Adverse Events of Special Interest (AESIs)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Adverse events of special interest for ipatasertib include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law
- Suspected transmission of an infectious agent by the study drug, as defined below:
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
  - Grade ≥ 3 fasting hyperglycemia
  - Grade ≥ 3 hepatotoxicity including ALT/AST elevations
  - Grade ≥ 2 colitis/enterocolitis
  - Grade ≥ 2 diarrhea
  - Grade ≥ 3 rash
  - Grade ≥ 2 pneumonitis

6.4 Adverse Event Management Guidelines

Guidelines for management of specific adverse events are provided in the subsections below.

6.4.1 Diarrhea Management Guidelines

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in Table 2. All patients should receive loperamide (2 mg oral twice a day or 4 mg once a day) as prophylaxis for diarrhea in the first cycle if allowed by local guidance, except when the Investigator approves omission (e.g., if there are clinical concerns that preclude the use of loperamide prophylaxis in the first cycle). Investigators are encouraged to continue this dosing for the remainder of the study, and the prophylaxis dose may be adjusted as necessary, using their discretion based on clinical judgment and per local guidance. If diarrhea occurs, it should be managed per guidelines; upon resolution or when

study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments (if allowed by local guidance).

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. Guidelines for treatment of diarrhea following the prophylactic dose of loperamide (where allowed) includes use of loperamide 2 mg every 4 hours or after each loose, watery stool, up to the maximum total dose of 16 mg/day or per institutional guidelines and standard of care, including, but not limited to, additional therapy with Lomotil® (diphenoxylate and atropine), codeine, or octreotide. Duration of diarrhea may be minimized by taking ipatasertib with food, avoiding lactose-containing foods, and hydrating with 8–10 glasses per day (~12 oz/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea that persists for more than 5 days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib, gastroenterologists should be consulted to rule out the risk of colitis and infection (e.g., obtaining CT images or a stool culture for infectious workup [Clostridium difficile, enteric bacteria, cytomegalovirus]). Patients should be educated on the symptoms and importance of early reporting of diarrhea to receive instructions of treatment and prevention of dehydration so that patients can be promptly and appropriately managed. Educational materials will be provided to investigators and patients outlining these guidelines.

Table 2 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• All patients should receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle, if allowed by local guidance or unless there is a clinical concern precluding their use. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.

Severity of Diarrhea [a]	Management Guideline
Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • Electrolytes (e.g., potassium and magnesium should be monitored as clinically indicated). • Manage with loperamide as early as possible 4 mg initially and then 2 mg every 4 hours or after every unformed stool until after 12-hour diarrhea free interval. • Dietary modifications, such as avoiding any lactose-containing foods and eating small meals. • Hydration with 8–10 glasses per day (~12 oz/glass) of clear liquid, such as broth or low-calorie drinks with electrolytes. • For non-infectious diarrhea lasting more than 48 hours despite optimal loperamide treatment, manage with second-line anti-diarrheal agents, including, but not limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce ipatasertib by one (or one additional) dose level for recurrent Grade 2 diarrhea. • Gastroenterologist consultation should be considered for diarrhea ≥gr 2 persisting despite maximal medical management and discontinuation of drug.When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 3 Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Electrolytes (e.g., potassium and magnesium should be monitored as clinically indicated). • Treat per Grade 2 management guidelines and supportive care. • Interrupt ipatasertib until diarrhea improves to Grade 1 or better. Ipatasertib should be reduced by one dose level when treatment is restarted. • For recurrent Grade 3 diarrhea, reduce ipatasertib dose by one additional dose level. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Table 2 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib/. A gastroenterologist consultation should be considered for diarrhea ≥gr 2 persisting despite maximal medical management and discontinuation of drug

ADL = activities of daily living; BID = twice a day; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; QD = once a day.

[a] Diarrhea, as defined by NCI CTCAE v5.0, A disorder characterized by an increase in frequency and/or loose or watery bowel movements.

6.4.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours. The treatment goals for glycemic control should be: 1) fasting glucose under 160 mg/dL and 2) HbA1c ≤8%.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see **Table 3**) and are intended to provide guidance for fasting glucose measurements assessed in the clinic. Decisions regarding study treatment should be made on fasting levels drawn in the clinic whenever possible.

In the event of ipatasertib interruption, anti-diabetic medications may need to be held or reduced (per investigator judgement) and glucose should be monitored closely to minimize the risk of hypoglycemia.

Because the hyperglycemia observed with ipatasertib treatment is consistently associated with endogenous elevations in insulin, insulin-based therapy to manage any hyperglycemia should be used with caution because severe hypoglycemic episodes could potentially occur. Therefore, initial treatment should be considered with biguanides (preferred), sulfonylureas, and other hypoglycemic treatments.

Table 3 Fasting Hyperglycemia Management Guidelines

Hyperglycemia	Management Guideline
General Guidance	Thoroughly evaluate all events of hyperglycemia for more common etiologies other than drug-induced effects. Investigate for diabetes. If patient has Type 1 diabetes, treat as an event of fasting glucose value 250–500 mg/dL. Workup could include confirmation of fasting blood glucose, urinary glucose and ketones, arterial blood gas, serum bicarbonate, hemoglobin A1C, C-peptide levels, anti-islet antibodies, and anti-GAD65 antibody. Treat hyperglycemia per institutional guidelines with fluid replacement, insulin, and correction of electrolyte abnormalities.
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) *	• Continue ipatasertib. • Provide patient with education on a diabetic diet and consider home glucose monitoring. • Consider oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia.
Fasting glucose value >160 to 250 mg/dL (> 8.9–13.9 mmol/L) *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤160 mg/dL. (Investigate for diabetes. If patient has Type 1 diabetes, treat as a fasting glucose value 250–500 mg/dL event. If patient does not have Type 1 diabetes, treat as per institutional guidelines.) • Encourage a diabetic diet and initiate home glucose monitoring. • Start oral anti-diabetic medications (e.g., metformin) or insulin replacement, guided by etiology of hyperglycemia. • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level (refer to Table 1). • If the patient previously has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Fasting glucose value 250 to 500 mg/dL (> 13.9–27.8 mmol/L) *	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤160 mg/dL and contact Medical Monitor. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Encourage a diabetic diet and initiate home glucose monitoring. • If the patient is already on an oral anti-diabetic medication, ipatasertib should be reduced by one dose level when treatment is restarted. • If previously, the patient has not been receiving any oral anti-diabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication. • If hyperglycemia 250–500 mg/dL recurs, the dose of ipatasertib should be reduced by one dose level (see Table 1) when treatment is restarted.
Fasting glucose value > 500 mgdL	• Withhold ipatasertib dosing until fasting glucose value resolves to ≤160 mg/dL.

(> 27.8 mmol/L); life-threatening consequences *	• Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Encourage a diabetic diet and initiate home glucose monitoring. • Upon recovery of fasting glucose to ≤160 mg/dL, reduce ipatasertib by one dose level (see Table 1) when treatment is restarted. • If glucose value > 500 mg/dL recurs, permanently discontinue ipatasertib and contact Medical Monitor. If glucose values are > 500 mg/dL discontinue ipatasertib. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib.

ULN=upper limit of normal.

* For all grades, the patient should receive education on a diabetic diet.

6.4.3 Neutropenia

Addition of hematopoietic growth factors is allowed. If a dose delay is required as a result of neutropenia at any grade, patients should receive prophylactic granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor per institutional standards. Patients should be counseled as to the risk of fever and infection and to the importance of contacting their treating physician immediately if these conditions occur so that they can be promptly and appropriately managed. Dosage modification guidelines for neutropenia and/or thrombocytopenia attributable to ipatasertib are outlined in **Table 4**.

Table 4 Neutropenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	Ipatasertib may be continued at the original dose.
Grade 3	• Ipatasertib should both be held until recovery to Grade 1 and if clinically appropriate based on the investigator's medical judgment to Grade 2 as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. – First episode: Reduce ipatasertib by one dose level. If recovery to Grade 1 is achieved with the use of G-CSF, then continued use of G-CSF is recommended once dosing of the study drug is resumed. – Recurrent episode: Ipatasertib should be reduced by one dose level when treatment is restarted.

Febrile neutropenia and Grade 4 neutropenia	• Ipatasertib should be held until recovery to Grade 1, and if clinically appropriate based on the investigator's medical judgment to Grade 2, as long as G-CSF is used to manage the neutropenia. Please see guidelines in this table regarding treatment for ongoing Grade 2 hematological toxicities. First episode: Ipatasertib should be reduced by one dose level when treatment is restarted. Recurrent episode: Ipatasertib should be discontinued. • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient will permanently discontinue ipatasertib treatment.

ANC = absolute neutrophil count; G-CSF= Granulocyte-colony stimulating factor.

6.4.4 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (i.e., prochlorperazine or metoclopramide per institutional guidelines; see **Table 5**). For persistent nausea and/or vomiting attributable to ipatasertib, dosage modification guidelines are outlined in **Table 5.**

Table 5 Nausea and Vomiting Management Guidelines

Severity of Nausea and /or Vomiting	Management Guideline
Grade 1	• Provide supportive care as needed.
Grade 2	• Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥ 3	• Interrupt ipatasertib until nausea or vomiting resolves to Grade 2 or better. • Provide maximum supportive care per local guidelines, with a minimum of two anti-emetics, including ondansetron. • If Grade ≥ 3 nausea or vomiting recurs, ipatasertib should be reduced by one dose level when treatment is restarted.

6.4.5 Hepatotoxicity

Permanently discontinue ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 × ULN and total bilirubin greater than 2 × ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria. Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see **Table 6**)

Table 6 Hepatotoxicity Management Guidelines

Severity of LFT Elevation	Management Guideline
Grade 1 AST or ALT > baseline –3 × ULN or T bilirubin > baseline –1.5 × ULN	Continue study drugs.
Grade 2 AST or ALT > 3–5 × ULN or T bilirubin > 1.5–3.0 × ULN	Continue study drugs. The frequency of liver function test monitoring should be increased as clinically indicated if the investigator judges that the laboratory abnormalities are potentially related to study medication.
Grade 3 AST or ALT > 5–20 × ULN or T bilirubin > 3–10 × ULN	Immediately interrupt ipatasertib. On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib/ reducing the dose by one level (refer to **Table 1**) Following treatment resumption, monitor serum transaminases and bilirubin at a minimum every 2 weeks for 3 months and monthly thereafter. If another Grade 3 event occurs, interrupt ipatasertib/. On return of LFTs to baseline or AST and ALT ≤2.5 x ULN and total bilirubin ≤1.5 x ULN levels, restart ipatasertib/, reducing the dose by one level Further Grade 3 occurrences must result in permanent discontinuation of ipatasertib.
Grade 4 AST or ALT > 20 × ULN or T bilirubin > 10 × ULN	Permanently discontinue ipatasertib.

LFT=liver function test; QD=once daily; ULN=upper limit of normal.

6.4.6 Rash

Treatment-related rash, has occurred in patients receiving ipatasertib treatment particularly when ipatasertib has been used certain combinations (eg ipatasertib in combination with paclitaxel and atezolizumab or with abiraterone). The following prophylaxis measures can be considered, in particular for combinations with overlapping skin toxicity.

- Unless contraindicated, daily PO antihistamine prophylaxis can be considered for at least the first cycle. It is suggested that a non-sedating longer-acting oral antihistamine be used (such as 10 mg of cetirizine PO QD or comparable dose of other antihistamines, e.g., loratadine, fexofenadine).

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity, including erythema multiforme, attributable to ipatasertib are shown below in

Table 7.

Table 7 Rash Management Guidelines

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs. • Consider topical corticosteroids.
Grade 2	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical corticosteroids. • Consider treatment of rash with oral corticosteroids.
Grade 3	• Interrupt ipatasertib treatment until resolution to Grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic corticosteroids. • Consider dermatological consultation. • If the skin toxicity resolves to Grade 1 or better or is no longer clinically significant within 28 days, following completion of the steroid taper, ipatasertib may be resumed at one dose level below the previous dose. • If recovery of the skin toxicity to Grade 1 or better does not occur or skin toxicity remains clinically significant continuously for 4 weeks, or Grade 3 rash recurs, permanently discontinue ipatasertib.
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

6.4.7 Pneumonitis

Pneumonitis is not known to be causally related to ipatasertib; however, it has been observed with other drugs treating pathways similar to ipatasertib. Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (see **Table 8**).

Table 8 Pneumonitis Management Guidelines

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every 8 weeks until a return to baseline.
Grade 2	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Consider resuming ipatasertib at same dose level or one dose level below per investigator's assessment. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. • For recurrent Grade 2 pneumonitis, ipatasertib must be resumed at one dose level below the previous dose. • Discontinue ipatasertib if recovery to Grade 1 or better is not evident within 28 days.
Grade 3	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Interrupt ipatasertib treatment until improvement to Grade 1 or better. Resume ipatasertib at one dose level below previous dose per investigator's assessment. If recovery to Grade 1 or better is not evident within 28 days, discontinue study treatments. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended. • For recurrent non-infectious Grade 3 pneumonitis events, ipatasertib should be permanently discontinued.
Grade 4	• If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe corticosteroids as clinically indicated. • Permanently discontinue ipatasertib. • Perform CT scan and PFTs. Repeat CT scan every 4 weeks until a return to baseline. Bronchoscopy is recommended.

CT = computed tomography; PFT = pulmonary function test.

6.4.8 Mucositis

Mouthwash such as magic mouth wash (if inaccessible, warm salt or bicarbonate water) should be used as supportive care per institution guidelines. Brushing teeth after meals, keeping lips moisturized with non-Vaseline® products, and avoiding alcohol, spicy food, and smoking have all been shown to reduce pain and infection related to mucositis. Ranitidine or omeprazole may be helpful if patients have epigastric pain. Dosage modification guidelines for mucositis attributable to study treatment are outlined in **Table 9**.

Table 9 Mucositis Management Guidelines

Severity of Mucositis	Management Guidelines
Grade 1 or 2	• Manage with maximum supportive care. • If Grade ≥ 2 mucositis recurs in subsequent 4-week cycles, despite maximal supportive care, the dose of ipatasertib should be reduced by one dose level.
Grade ≥ 3	• Hold ipatasertib until recovery to Grade 2 or better. If the mucositis resolves to Grade 2 or better during the current cycle, the dose of ipatasertib should be reduced by one dose level. • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue ipatasertib.

6.4.9 Other Non-Hematologic Toxicities

If other Grade ≥3 non hematologic toxicities not described above develop in patients, treatment with ipatasertib may be held, depending on the attribution of the toxicity, at the discretion of the investigator.

If the toxicity resolves to Grade 1 or better within 2 weeks, treatment may resume with the attributable agent.

If the toxicity resolves to Grade 1 or better in 2–3 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines

.

Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes >3 weeks, treatment may resume with the attributable agent with dose reduction, or the attributable agent may be permanently discontinued, at the discretion of the investigator and after discussion with the Medical Monitor.

6.5 Paclitaxel and carboplatin Dose Modification and Supportive Care Guidelines for Drug-Related Adverse Events

Agent	Starting Dose	Dose -1	Dose -2
paclitaxel	175mg/m^2	135mg/m^2	110mg/m^2
carboplatin	AUC 5	AUC 4	NA

Subsequent courses of treatment which contain cytotoxic chemotherapy (paclitaxel and/or carboplatin) will not begin (day 1 of each cycle) until the ANC is ≥ 1,000 and the platelet count is ≥ 100,000.

Filgrastim, pegfilgrastim or biosimilars can be used per treating investigators discretion and/or institutional, NCCN and/or ASCO guidelines.

Dose limiting hematologic toxicities are defined as:

- Febrile neutropenia
- Prolonged grade 4 neutropenia persisting for greater than 7 days
- Grade 4 thrombocytopenia (platelet count <25,000)
- Bleeding associated with grade 3 thrombocytopenia (25,000 to <50,000)

Dose modification for dose limiting hematologic toxicity or cycle delay > 7 days due to hematologic toxicity:

ANC	PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Add filgrastim, pegfilgrastim or biosimilar	Reduce paclitaxel one dose level	Reduce paclitaxel one more dose level
Yes	Yes	Add filgrastim, pegfilgrastim or biosimilar AND reduce carboplatin one AUC unit	Reduce paclitaxel one dose level	Reduce paclitaxel one more dose level
No	Yes	Reduce carboplatin one AUC unit	Reduce carboplatin one more AUC unit	Reduce paclitaxel one dose level

Note: For patients meeting criteria for dose modification after third recurrence, notify study chair

Peripheral neuropathy: for grade 2 (or greater) peripheral neuropathy:
Hold paclitaxel until recovered to grade 1, then paclitaxel should be reduced one dose level. Chemotherapy can be delayed for a maximum of 3 weeks. If neuropathy does not recover to grade 1, paclitaxel should be omitted from subsequent cycles.

Renal toxicity: Renal toxicity is not expected from paclitaxel and/or carboplatin as a direct complication of chemotherapy in this patient population given the required treatment free interval in the pre-treated population. As such, there are no specific dose modifications for renal toxicity. However, see Appendix IV for carboplatin dose calculation instructions for criteria for recalculation of dose.

Hypersensitivity reaction: In general, the occurrence of a hypersensitivity reaction to paclitaxel and/or carboplatin can be managed with administration of medication to prevent hypersensitivity reactions and/or adjustments in infusion rates, per institutional standards. If patient experiences hypersensitivity reaction that requires discontinuation of paclitaxel and/or carboplatin, the patient will discontinue protocol directed treatment. If this occurs prior to completion of cycle 1 treatment, patient will be replaced and deemed as DLT-inevaluable.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY027 is Ipatasertib (NSC#781451), which is being made available under an IND sponsored by DCTD, NCI

Commercial Agents

The commercial agents in NRG-GY027 *are Paclitaxel (NSC #125973)* and *Carboplatin (NSC #201345).*

Since patients are receiving investigational and commercial agents on the same treatment are, Investigationl Agent reporting guidelines will apply. To determine whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4.2 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

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

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

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

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipatasertib (NSC 781451)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Ipatasertib (NSC 781451)

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 188 patients.* Below is the CAEPR for Ipatasertib.

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 2.0, September 16, 2021[1]

Adverse Events with Possible Relationship to Ipatasertib (CTCAE 5.0 Term) [n= 188]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis	
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Mucositis oral	
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatotoxicity)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 2)***
INVESTIGATIONS			
		Neutrophil count decreased	
		Platelet count decreased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		***Dysgeusia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			

Adverse Events with Possible Relationship to Ipatasertib (CTCAE 5.0 Term) [n= 188]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Erythema multiforme	
	Rash[2]		*Rash[2] (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]Rash may include rash with or without pruritus, toxic skin eruption, and rash maculo-papular.

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

CARDIAC DISORDERS - Cardiac arrest
GASTROINTESTINAL DISORDERS - Abdominal distension; Gastroesophageal reflux disease
INFECTIONS AND INFESTATIONS - Skin infection
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Cholesterol high; Investigations - Other (blood insulin increased); Investigations - Other (glucose urine present)
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypertriglyceridemia; Hyperlipidemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myalgia
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Paresthesia
RENAL AND URINARY DISORDERS - Acute kidney injury; Glucosuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Skin and subcutaneous tissue disorders - Other (toxic skin eruption)
VASCULAR DISORDERS - Hypotension; Thromboembolic event

Note: Ipatasertib 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.

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 link in RAVE or via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers.

Submitting a report via CTEP-AERS serves as notification to NRG 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.

7.4.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by CTEP as the IND sponsor for this study and by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page; fax supporting documentation to CTEP at 301-897-7404 and contact NRG Regulatory Affairs at 215-854-0716 for source documentation assessment.
- 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.

7.4.2 Expedited Reporting Requirements for Adverse Events

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

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

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

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

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes

Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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 CTEP-AERS 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 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[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

7.4.3 Reporting to the Site IRB/REB

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

7.4.4 Secondary Malignancy:

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

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

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

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

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

7.5 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 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

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 Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

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.

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

8.1 Cancer Trials Support Unit Registration Procedures

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 email or calling 1-888-651-CTSU (2878).

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

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

Additional Requirements

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

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

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

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and

- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements
Additional requirements to obtain an approved site registration status include:
- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents

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

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
  - Enter the protocol number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select *NRG*, and protocol number *NRG-GY027*.
- Click on *Documents, Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents

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

To access the Regulatory Submission Portal log 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. **(22-DEC-2023).**

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 describes DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List. **(22-DEC-2023)**

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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the 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.

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

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 5.3)

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 Investigational Study Agent: Ipatasertib (GDC-0068) (NSC # 781451, IND # [redacted]

Chemical Name: [(*S*)-2-(4-chlorophenyl)-1-(4-((5*R*,7*R*)-7-hydroxy-5-methyl-6,7-dihydro-5*H*-
cyclopenta [*d*]pyrimidin-4-yl)piperazin-1-yl)-3-(isopropylamino) propan-1-one

Other Names: *GDC-0068*

Classification: AKT inhibitor

Molecular Formula: C24H32ClN5O2 **M.W.:** 458.00 g/mol as free base
494.46 g/mol as mono-HCl salt

Approximate Solubility: The apparent solubility of ipatasertib drug substance is high (> 10 mg/mL) across a pH range of 1.1-7.0.

Mode of Action: Ipatasertib is a potent, selective, ATP-competitive small-molecule inhibitor of all three isoforms of Akt. Ipatasertib selectively binds to the active conformation of Akt and inhibits its kinase activity.

Description: Ipatasertib drug substance is a white-to-tan powder.

How Supplied:
Genentech supplies and CTEP, DCTD, NCI distributes ipatasertib as 100 mg or 200 mg oval, film-coated tablets in a 30 count bottle. The 100 mg tablet is greyish yellow and the 200 mg tablet is brownish pink. In addition to the ipatasertib drug substance, each tablet contains microcrystalline cellulose, pregelatinized maize starch, croscarmellose sodium, colloidal silicon dioxide, povidone, magnesium stearate and either Opadry II Yellow film coat (100 mg) or Opadry II Pink film coat (200 mg).

Storage: Do not store above 25°C / 77°F

If a storage temperature excursion is identified, promptly return ipatasertib to less than 25°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

Route of Administration: oral

Method of Administration: Ipatasertib can be administered without regard to food.

Potential Drug Interactions:
Ipatasertib is primarily metabolized by CYP3A and is a substrate of P-glycoprotein. Strong inhibitors and inducers of CYP3A may result in increased or decreased ipatasertib exposures, respectively. The following drugs should be avoided, or used with caution when administering ipatasertib. If using of one of these drugs is necessary, the risks and benefits should be evaluated prior to its concomitant use with ipatasertib:

- Strong CYP3A inhibitors: such as but not limited to atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir,

saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements
- Strong CYP3A inducers: such as but not limited to rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- Ipatasertib is a moderate inhibitor of CYP3A4. CYP3A4 substrates with a narrow therapeutic index: such as but not limited to alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine should be avoided or administered with caution.

Patient Care Implications:
- Because the PI3K-Akt-mTOR pathway is involved in glucose metabolism, inhibition of this signaling network and its target mTOR can cause hyperglycemia, which is a toxicity common to the class of PI3K-Akt-mTOR inhibitors.
- Agents such as proton pump inhibitors (e.g., omeprazole, pantoprazole) are not expected to affect ipatasertib PK.
- Ipatasertib is not expected to prolong the QTc interval.

9.2 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)*

9.3 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. 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.

9.3.1 Investigator Brochure Availability

The current versions of the Ipatasertib (NSC # 781451) IB 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.

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

9.4 Commercial Agent—Carboplatin

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug for pharmacologic information, drug preparation, handling, and storage.

9.4.1 Product Description

Carboplatin is commercially available. Carboplatin aqueous solution injection is a premixed aqueous solution of 10 mg/mL carboplatin. Dosage forms include **50mg**/5mL, **150 mg**/15mL, **450 mg**/45mL and **600 mg**/60 mL aqueous solution in multidose vials.

9.4.2 Solution Preparation

See the carboplatin package insert for preparation instructions.

9.4.3 Availability/Supply

Carboplatin is obtained by the investigator from commercial supply.

9.4.4 Adverse Events

Hair loss, Vomiting/Nausea, Infection, Anemia, Bruising/Bleeding, Belly pain, Diarrhea/Constipation, Peripheral Neuropathy, Allergic Reaction.

Please refer to the package insert or current Health Canada approved product monograph and the site-specific pharmacy for toxicity and safety information.

9.5 Commercial Agent—Paclitaxel

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug for pharmacologic information, drug preparation, handling, and storage.

9.6.1 Adverse Events

Please refer to the package insert and the site-specific pharmacy for toxicity and safety information.

9.6.2 Availability/Supply

Paclitaxel is obtained by the investigator from commercial supply.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Review

Not applicable

10.2 Integral Biomarkers

Not applicable

10.3 Integrated Biomarkers (24-APR-2023)

A detailed description of the integrated biomarker testing can be found in the Correlative Science Appendix (Appendix VIII).

10.3.1 Ipatasertib Pharmacokinetics

10.3.1.1 Integrated Biomarker to be Tested

Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

No review required

10.3.1.2 Integrated Biomarker Assay Summary

Frozen plasma (at least 500µL) and snap-frozen IDS tumor and normal tissue (250mg each) will be used for LC-MS/MS. The EET Biobank will batch ship frozen plasma aliquots and tissue to the Analytical Pharmacology Core (City of Hope) at study closure. Ipatasertib and its active metabolite, M1, will be measured using an LC-MS/MS assay developed and validated in the U24-funded PITT-CAL PK Resource Laboratory under the supervision of Dr. [redacted] at the City of Hope.

10.3.1.3 Integrated Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.3.2 Whole Exome Sequencing

10.3.2.1 Integrated Biomarker to be Tested

Whole exome sequencing (WES)

National Clinical Laboratory Network (NCLN) approved

10.3.2.2 Integrated Biomarker Assay Summary

DNA extracted from pre-treatment archival FFPE tumor tissue and whole blood will be used for WES. The EET Biobank perform a pathology QA review and macrodissect tumor tissue only when needed to enrich tumor content. The EET Biobank will then co-extract DNA and RNA from tumor tissues following NCLCN standard operating procedures (SOPs). DNA and RNA will be stored in a -80°C freezer until distribution. The remaining FFPE block and H&E stained slide(s) will be stored at room temperature **(22-DEC-2023).** For this assay, the EET Biobank will batch ship aliquots of DNA to the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) at study closure. WES will be done as per NCI-approved NCLN SOPs under the supervision of Dr. [redacted].

10.3.2.3 Integrated Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.3.3 RNAseq

10.3.3.1 Integrated Biomarker to be Tested

RNAseq

National Clinical Laboratory Network (NCLN) approved

10.3.3.2 Integrated Biomarker Assay Summary

RNA extracted from pre-treatment archival FFPE tumor tissue will be used for RNAseq. The EET Biobank will batch ship aliquots of RNA to the NCLN Genomics Laboratory or MoCha, Frederick National Laboratory for Cancer Research (FNLCR) at study closure. **(22-DEC-2023)** RNAseq will be done as per NCI-approved NCLN SOPs under the supervision of Dr. [redacted]

10.3.3.3 Integrated Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.3.4 PTEN Loss

10.3.4.1 Integrated Biomarker to be Tested

PTEN IHC

Biomarker Review Committee (BRC) approved

10.3.4.2 Integrated Biomarker Assay Summary

Three unstained slides (charged, 4µm) from archival FFPE pre-treatment tumor tissue will be

used for PTEN loss IHC. The EET Biobank will batch ship fresh-cut unstained sections on glass slides (within 48 hours of sectioning) to the Clinical Immunohistochemistry Laboratory (MD Anderson Cancer Center) at study closure. Following IHC done under the supervision of Dr. [redacted], quantification will be performed using Aperio-Leica Scanscope-associated algorithms. H-score will be determined as the product of the staining intensity (0, absent; 1, weak staining; 2, moderate staining; and 3, strong staining) multiplied by the percentage of positive cells quantified.

10.3.4.3 Integrated Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.4 Biospecimen Submission Tables

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

10.4.1 Mandatory Biospecimen Submissions

The patient agrees to participate in mandatory biospecimen collection as part of the main trial. Participating sites are required to submit the patient's biospecimens and accompanying documentation as outlined below.

Biospecimens should not be shipped until after patient registration and Bank ID assignment.

Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship to
PRE-TREATMENT		
FFPE – Submit *one* (listed in order of preference)		
Archival FFPE Pre-Treatment Metastatic Tumor (FM01) *or* FFPE Pre-Treatment Primary Tumor (FP01)[1] Block must be submitted[2]	Pre-treatment tumor collected from laparoscopy (preferred) or five 18G cores (embedded in one block) by radiology or interventional radiology (acceptable)	EET Biobank within 8 weeks of registration[3]
Blood Biospecimens		
Pre-Treatment Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to study treatment	EET Biobank the day collected
INTERVAL DEBULKING SURGERY		
FFPE – Submit *one* (listed in order of preference)		
Archival FFPE IDS Metastatic Tumor (FM02) *or* FFPE IDS Primary Tumor (FP02)[1] Block must be submitted[2]	Collected at interval debulking surgery (IDS); if possible, IDS tumor tissue should be collected from the same site as the pre-treatment tumor tissue *Optional:* If IDS not done and biopsy done as SOC, submit biopsy	EET Biobank within 20 weeks of registration[3]
Frozen Tissue– Submit normal tissue and *one* tumor type (listed in order of preference)		
Snap-Frozen Normal Tissue (RN02)[1] 250mg preferred (minimum 100mg)	Collected at interval debulking surgery (IDS); if	EET Biobank within 14 weeks of

Snap-Frozen Metastatic Tumor (RM02) *or* Snap-Frozen Primary Tumor (RP02)[1] 250mg preferred (minimum 100mg)	possible, IDS tumor tissue should be collected from the same site as the pre-treatment tumor tissue	registration[3]
Blood Biospecimens		
IDS Plasma (PB01) prepared from 7-10mL drawn into purple top (EDTA) tube(s)	Collected at interval debulking surgery (IDS)	EET Biobank within 14 weeks of registration[3]

1 A partially redacted copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the EET Biobank. See Appendix VII for redaction guidelines.
2 Only blocks will be accepted. Please provide Appendix VII to your pathologist.
3 EET Biobank / Protocol NRG-GY027, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.4.2 Optional Biospecimen Submissions

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

Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship to
PRE-TREATMENT		
Frozen Tissue – Submit *one* tumor type (listed in order of preference)		
Archival Snap-Frozen Normal Tissue (RN01)[1] 250mg preferred (minimum 100mg)	Prior to study treatment	EET Biobank within 14 weeks of registration[2]
Archival Snap-Frozen Metastatic Tumor (RM01) *or* Archival Snap-Frozen Primary Tumor (RP01) 250mg preferred (minimum 100mg)[1]		
Blood Biospecimens		
Baseline CyTOF Whole Blood (WB03) 5mL drawn into green top (sodium heparin) tube(s), processed with PROT1 buffer, and frozen[3]	Prior to study treatment	EET Biobank within 14 weeks of registration[2]
INTERVAL DEBULKING SURGERY		
Blood Biospecimens		
IDS CyTOF Whole Blood (WB04) 5mL drawn into green top (sodium heparin) tube(s), processed with PROT1 buffer, and frozen[3]	Collected at interval debulking surgery (IDS)	EET Biobank within 14 weeks of registration[2]

1

A partially redacted copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the EET Biobank . See Appendix VII for redaction guidelines.
2 EET Biobank / Protocol NRG-GY027, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org
3 Refer to Appendix VII for CyTOF Whole Blood special processing instructions

10.4.3 Biospecimen Prioritization for Biomarker Testing

Priority	Assay	Biomarker	Biospecimen Requirement	NCI Approval
EDTA Whole Blood				
1	WES	Integrated	Yes for DNA	NCLN approved
CyTOF Whole Blood				
1	CyTOF	Exploratory	Whole blood with PROT1	No†

FFPE				
1	WES	Integrated	Yes for DNA*	NCLN approved
2	PTEN loss	Integrated	3 (charged, 4um)	BRC approved
3	RNAseq	Integrated	Yes for RNA*	NCLN approved
4	pS6, pGSK3B, pPRAS40	Exploratory	8 (charged, 5um)	No review required
Frozen Tissue				
1	LC-MS/MS	Integrated	250mg	No review required
2	RPPA	Exploratory	2-3 (uncharged, 8um)	No†
Plasma				
1	LC-MS/MS	Integrated	500µL	No review required

†*Testing of banked biospecimens will not occur until an amendment to this protocol (or a separate correlative science proposal) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.*
*DNA/RNA co-extraction **(24-APR-2023)**

10.5 Exploratory Biomarkers

10.5.1 Pharmacodynamics

10.5.1.1 Exploratory Biomarker to be Tested

pPRAS40 immunohistochemistry (IHC)

BRC review required

10.5.1.2 Exploratory Biomarker Assay Summary

Three unstained slides (charged, 5µm) from archival formalin-fixed, paraffin-embedded (FFPE) pre-treatment and interval debulking surgery (IDS) tumor tissue will be used for pPRAS40 IHC. The EET Biobank will batch ship fresh-cut sections to the Gutkind Laboratory (Moores Cancer Center, University of California San Diego) at study closure. Following IHC, quantification will be performed using Aperio-Leica Scanscope-associated algorithms. H-score will be determined as the product of the staining intensity (0, absent; 1, weak staining; 2, moderate staining; and 3, strong staining) multiplied by the percentage of positive cells quantified.

10.5.1.3 Exploratory Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.5.2 Treatment Effects on AKT Pathway (24-APR-2023)

10.5.2.1 Exploratory Biomarker to be Tested

pS6 and pGSK3B immunohistochemistry (IHC)

No review required

10.5.2.2 Exploratory Biomarker Assay Summary

Five unstained slides (charged, 5µm) from archival formalin-fixed, paraffin-embedded (FFPE) archival/baseline and interval debulking surgery (IDS) tumor tissue will be used for pS6 and pGSK3B IHC. The EET Biobank will batch ship fresh-cut unstained sections on glass slides (within 48 hours of sectioning) to the Gutkind Laboratory (Moores Cancer Center, University of California San Diego) at study closure. Following IHC, quantification will be performed using

Aperio-Leica Scanscope-associated algorithms. H-score will be determined as the product of the staining intensity (0, absent; 1, weak staining; 2, moderate staining; and 3, strong staining) multiplied by the percentage of positive cells quantified.

10.5.2.3 Exploratory Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.5.3 Immune Cell Subsets

10.5.3.1 Exploratory Biomarker to be Tested

CyTOF

Testing of banked biospecimens will not occur until an amendment to this protocol (or a separate correlative science proposal) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies. **(24-APR-2023)**

10.5.3.2 Exploratory Biomarker Assay Summary

Baseline and IDS whole blood will be used for CyTOF. Upon approval, the EET Biobank will batch ship CyTOF whole blood with PROT1 to Dr. [redacted] at study closure. These biospecimens will undergo a next generation of single-cell analysis technology called mass cytometry, which overcomes the limitations of flow cytometry (i.e., measuring a maximum of ten markers per panel). The CyTOF is a mass spectrometer-flow cytometer hybrid instrument that uses stable isotopes instead of fluorophores as reporters.

10.5.3.3 Exploratory Biomarker Results Reporting

Dr. [redacted] will provide biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results.

10.5.4 Protein pathway activation mapping of the AKT-mTOR signaling pathway by LCM-RPPA (24-APR-2023) 10.5.4.1 Exploratory Biomarkers to be Tested (24-APR-2023)

Twenty-three members of the AKT-mTOR protein signaling pathway will be quantitatively measured by LCM-RPPA based analysis of the pre-treatment baseline FFPE tissue samples. See Appendix VIII, Section 2.2 for details.

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

10.5.4.2 Exploratory Biomarker Assay Summary

Pre-treatment and IDS tumor tissue will be used for LCM-RPPA. Upon approval and provided that sufficient FFPE materials remain, the EET Biobank will batch ship 2-3 8µm fresh-cut uncharged sections of archival FFPE tumor tissue to the Center for Applied Proteomics and Molecular Medicine (George Mason University) at study closure. Multiple members (. See Appendix VIII, Section 2.2 for details.) of the AKT-mTOR signaling pathway including phosphorylated AKT S473 and T308 will be measured using the LCM-RPPA workflow

originated in the Petricoin-Liotta lab and under the supervision of Dr. [redacted]. **(24-APR-2023)**

10.5.4.3 Exploratory Biomarker Results Reporting

Dr. [redacted] will provide all RPPA biomarker results to the NRG SDMC for analysis. Sites will not receive biomarker results. **(24-APR-2023)**

10.6 Banking Biospecimens for Future Research

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

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

11. ASSESSMENT OF EFFECT

11.1 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.

11.1.1 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.

11.1.2 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.

11.2 Response Criteria

Determination of response should take into consideration all target (See 11.2.1) and non-target lesions (See 11.2.2).

11.2.1 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.

11.2.2 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).

11.2.3 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	Biomarker CA-125	New Lesions*	Time Point Response
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	NE	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	Any value	Yes	PD

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

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

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

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

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

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

11.2.4 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-GY027, 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.

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.

11.3 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.

11.4 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, or date of last contact if neither progression nor death has occurred.

11.5 Survival

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

12. DATA AND RECORDS

12.1 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:

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

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as 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. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management* > *Rave section* or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

12.2 NRG Data Management Forms

Refer to the CTSU member website for protocol Form Set.

12.3 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 sections 7.4 and section 7.5. for information about expedited and routine reporting.

12.4 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**.

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

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

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

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

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

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

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

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

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

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

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

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

12.5 Data Quality Portal

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

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

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

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms

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

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

12.6 Global Reporting/Monitoring

DMU Complete *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 Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data 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.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a single arm, open label, limited multi-center, phase I study of ipatasertib in combination with paclitaxel and carboplatin as neoadjuvant chemotherapy in patients with newly diagnosed ovarian cancer. A total of 4 dose levels of ipatasertib are planned: 200 mg (DL1), 300 mg (DL2), 400 mg (DL3), and a DL-1 of 100 mg.

This trial has two phases: a dose-escalation phase to estimate the maximum tolerated dose (MTD) of ipatasertib, and an expansion phase in which the feasibility will be further to be examined after the MTD is established. This trial has a sample size ranging from 21 to 36.

The dose-escalation phase will follow a standard 3+3 design with dose escalation and de-escalation to estimate the MTD based on dose-limiting toxicities (DLTs) that occur in the first cycle beginning with dose level 1. DLT window is 1 cycle = 21 days.

The expansion phase will utilize a single-stage design with a total of 18 patients treated at the MTD including the 6 patients during dose escalation and the 12 at dose expansion).

The dose escalation phase indicated Dose Level 1 as the MTD. Based on the safety data review by the study team and CTEP, patients enrolled to the expansion phase will be treated at Dose Level 1 (See Section 5 Table 1) **(22-DEC-2023).**

13.2 Stratification and Randomization

There is no stratification and randomization.

13.3 Study Endpoints

13.3.1 Primary Endpoints

1) DLTs that occur within the first cycle of neoadjuvant chemotherapy (as defined in Section 5.4) in the dose escalation phase.
2) DLTs that occur within the first cycle of neoadjuvant chemotherapy (as defined in Section 5.4) in the expansion phase.
3) The frequency and severity of adverse events as assessed by CTCAE v5.

13.3.2 Secondary Endpoints

1) Tumor response (partial or complete) assessed by RECIST 1.1.

13.3.3 Translational Research Endpoints

1) Measurements for pPRAS40 expression in the pre-treatment tumor and on-treatment tumor.
2) Measurements of tissue and blood pharmacokinetics for ipatasertib.
3) Tumor response assessed by RECIST 1.1, and measurements for genomic alterations in PI3K Pathway genes (PTEN, PI3KCA, PIK3R1, AKT1, p53 loss, KRAS, NF1, TSC1/TSC1).
4) Tumor response assessed by RECIST 1.1, and measurements for transcriptomic alterations in PI3K Pathway genes (PTEN, PI3KCA, PIK3R1, AKT1, p53 loss, KRAS, NF1, TSC1/TSC1).
5) Tumor response assessed by RECIST 1.1, and measurement for PTEN loss.
6) Tumor response assessed by RECIST 1.1, and measurements for the 23 individual AKT-mTOR protein pathway activation mapping proteins/phosphoproteins measured by LCM-RPPA listed in **10.5.4.1. (24-APR-2023)**

13.4 Primary Objectives Study Design

13.4.1 Primary Hypothesis and Endpoints

Primary hypothesis for dose escalation phase: Ipatasertib can be safely combined with paclitaxel and carboplatin as neoadjuvant chemotherapy in patients with newly diagnosed ovarian cancer.

Primary hypothesis for expansion phase: The study regimen will be considered feasible if the probability of a patient experiencing a DLT in cycle 1 is 15% or less. The study

treatment is considered infeasible if the probability of a patient experiencing a DLT in cycle 1 is 35% or higher.

Primary endpoints: see Section 13.3.1.

13.4.2 How Primary Endpoints Will be Analyzed

The primary study objectives are to estimate the MTD in dose-escalation phase and to evaluate the feasibility in expansion phase once the MTD is established for ipatasertib in combination with paclitaxel and carboplatin as neoadjuvant chemotherapy for ovarian cancer. This study consists of two phases with a sample size ranging from 21 to 36 patients: a dose-escalation phase for estimation of the MTD (PART I) and expansion phase (PART II).

Dose-Escalation Phase (Part I)

A standard 3+3 with dose de-escalation design will be used to determine the MTD. Patients will be accrued in cohorts of size 3. DLTs will be evaluated during the first 21-day cycle. The dose level combinations and orders are presented in Section 5 Table 1.

The starting dose level (Dose Level 1, DL1) will consist ofpaclitaxel 175mg/m^2 every 21 days, carboplatin (AUC 5), and ipatasertib at 300 mg po daily.

For DLT evaluation purpose, a patient is treated as having completed the first cycle of neoadjuvant chemotherapy if this patient completes at least 80% of ipatasertib out the 21 daily ipatasertib doses.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **related** to ipatasertib toxicity of any grade will be considered a DLT by the definition in 5.4.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **unrelated** to ipatasertib toxicity of any grade will be considered for replacement after discussion with CTEP, and these patients deem to be DLT-unevaluble. The reason for not completing the cycle needs to be determined and well annotated.

Dose escalation rules are outlined in Section 5.5.
Safety data will be reviewed with CTEP prior to opening expansion phase.

Expansion Phase (Part II)

Once the MTD is determined from the dose-escalation phase, that dose will be used for the feasibility phase unless clinical judgement indicates that a lower dose be used. DLTs will be based the first 21-day cycle.

For DLT evaluation purpose, a patient is treated as having completed the first cycle of neoadjuvant chemotherapy if this patient completes at least 80% of ipatasertib out the 21 daily ipatasertib doses.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **related** to ipatasertib toxicity of any grade will be considered a DLT by the definition in 5.4.

Patients who miss 5 or more doses of ipatasertib (less than 80% of the dosage cycle) **unrelated** to ipatasertib toxicity of any grade will be considered for replacement after discussion with CTEP, and these patients deem to be DLT-unevaluble. The reason for not completing the cycle needs to be determined and well annotated.

Twelve additional patients will be treated at the MTD for a total of 18 patients treated at that dose. If 5 or fewer out of these 18 patients have DLTs in the first cycle of neoadjuvant chemotherapy, then the regimen will be considered feasible for further evaluation, otherwise the regimen will be considered infeasible.

Among these 12 participants enrolled in the expansion phase, it is anticipated that 10 participants will have evaluable biopsies for evaluation of the change of pPRAS40 based on prior clinical trials in which 10% will not have interval debulking surgery. These 10 patients with evaluable biopsies will provide a 90% power to detect a decrease of 1 standard deviation in pPRAS40 after neoadjuvant treatment by a one-sided paired t-test at 0.05 significance level.

For the overall evaluation of adverse events, all patients who receive any study drug will be evaluable. For DLT evaluation, the DLT-evaluable patients will only include those eligible patients who have a DLT within the first cycle of neoadjuvant chemotherapy, or complete the first cycle of neoadjuvant chemotherapy.

The estimation of the MTD and the determination of the feasibility is integrated in the design. The number of patients with DLTs will be summarized by dose level. Frequency and severity of adverse events as assessed by CTCAE v5 will be tabulated as descriptive statistics.

13.4.1 Sample Size and Power Calculations

Dose escalation phase

A minimum of 9 patients and a maximum of 24 patients will be treated in the dose-escalation phase.

The table below summarizes the probabilities of dose escalation and de-escalation in a standard 3+3 design for a range of true DLT rates

True DLT rate	10%	20%	30%	40%	50%
Probability of dose escalation	0.91	0.71	0.49	0.31	0.17
Probability of dose de-escalation	0.09	0.29	0.51	0.69	0.83

Expansion phase

A total of 18 patients will be treated at the MTD including the patients treated at the

MTD in the dose-escalation phase. Expansion phase has 88% probability of correctly declaring the regimen feasible and 81% probability of correctly declaring it infeasible with the feasibility decision rules.

13.5 Study Monitoring of Primary Objectives

During trial, all enrolling sites will be required to participate in a regularly scheduled teleconference including the study chairs, and phase I committee chair, study statistician, data management, and protocol administrator. DLTs and other toxicities will be discussed among this protocol monitoring team. The decision to de-escalate or escalate is made by consensus of the study team in accordance with the decision rules outlined in the protocol.

NRG Oncology Data Monitoring Committee (DMC)

The NRG Oncology DMC will review the study twice a year with respect to patient accrual and AEs. The DMC also will review the study for protocol-specified interim analyses and on an "as needed" basis.

NRG Early Phase Oversight Committee

Study reports focusing on accrual and adverse event data will be prepared regularly and the PI/NRG study team will have regular conference calls (biweekly or at most monthly) to review the accrual/safety data. Information from these calls will be reviewed quarterly by the NRG Oncology Early Phase Oversight Committee.

13.6 Accrual/Study Duration Considerations

This study population is similar to patients in NRG-GY007 opened in May 2016. The phase I accrual rate was approximately 1.4 patients per month for NRG-GY007. The projected accrual rate for this trial is 2 patient per month.

The duration of accrual for the dose-escalation phase is a function of the unknown dose-toxicity relationship and the resulting number of dose levels required.

The duration of accrual for the feasibility phase is approximately at least 6 months. The duration of neoadjuvant chemotherapy is 9 weeks, and it will be about 3 to 4 weeks up to 6 weeks before patients have interval debulking surgery. The duration of follow-up is 30 days after last dose of ipatasertib. The analysis for primary objectives can be accomplished within 4 - 7 months of final patient entry. The analysis including secondary objectives will require distribution of biospecimens, resolution of queries, completion of all laboratory tests, and collation of laboratory data with clinical data. These can be accomplished within 7-13 months of final patient entry.

13.7 Dose Level Guidelines

A standard 3+3 with dose de-escalation design will be used for regimens in this study. See section 5.5 for details. Definition of DLTs is in section 5.4.

13.8 Secondary Endpoints and Analysis Plans

13.8.1 Secondary Hypotheses and Endpoints

The secondary objectives focus on estimation and description; there are no specific hypotheses.

Secondary endpoints see section 13.3.2.

13.8.2 Definitions of Secondary Endpoints and How These Will Be Analyzed
Tumor response is assessed by RECIST 1.1, and will be summarized by dose level. The proportion of patients with objective tumor response will be estimated with their corresponding 90% confidence interval for expansion phase.

13.9 Translational Research Endpoints

13.9.1 Integrated Endpoints (24-APR-2023)

The Ipatasertib pharmacokinetics will be summarized by protocol-specified collection time, dose level and bio-speciment type, and a mixed model will be used to identify the maximum concentration (Cmax) in plasma and tumor tissue whenever it is feasible.

Genomic alterations in PI3K Pathway genes for each biomarker of PTEN, PI3KCA, PIK3R1, AKT1, p53 loss, KRAS, NF1, TSC1/TSC1 from archival FFPE will be summarized and tabulated. The correlations of tumor response with genomic alterations for each of these biomarkers will be assessed by 1-sided Spearman's rank correlation coefficient tests at 10% signiciance level, respectively. The maximum sample size of 18 in expansion phase will provide 90% power to detect a rank correlation coefficient as 0.6 at 10% significance level (Figure 13.1).

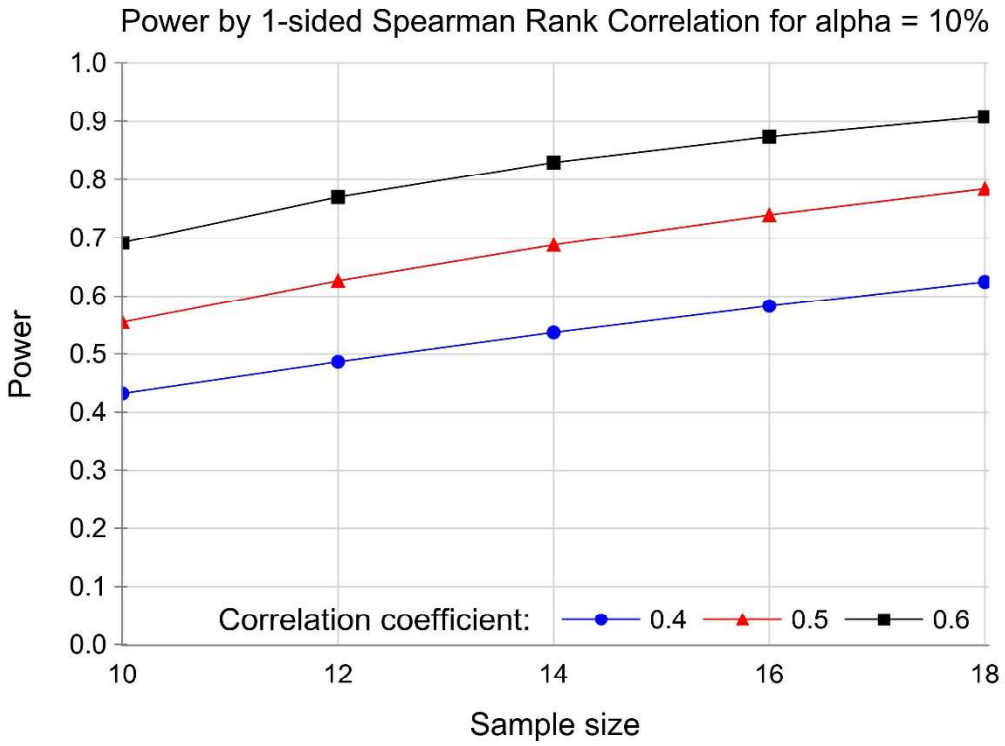

Figure 13.1

Similarly, transcriptomic alterations in PI3K Pathway genes for each biomarker of PTEN, PI3KCA, PIK3R1, AKT1, p53 loss, KRAS, NF1, TSC1/TSC1 from archival FFPE will be summarized. The associations of tumor response with transcriptomic alterations for each of these biomarkers will separately be evaluated by 1-sided Spearman's rank correlation coefficient tests at 10% signiciance level.

The proportion of patients who have PTEN loss by IHC from archival FFPE will be estimated with the corresponding 90% confidence interval. The correlation between PTEN loss by IHC and tumor response will be tested by 1-sided Spearman's rank correlation coefficient tests at 10% signiciance level.

13.9.2 Exploratory Endpoints (24-APR-2023)

pPRAS40 expression in tumor will be summarized by collection time point and dose level. Wilcoxon signed rank test will be used to explore the change of pPRAS40 expression in the pre-treatment vs on-treatment tumor in the patients who have been treated at the MTD and have evaluable biopsy specimen.

Quantitative phosphorylated AKT S473 and T308, which are part of the 23 AKT-mTOR signaling pathway activation proteins obtianed LCM-RPPA from tumor tissue will be summarized by collection time point and dose level (see Appendix VIII, Section 2.2 for details). Spearman rank correlation coefficient tests will be used to investigate the associations of tumor response with baseline phosphorylated expression for AKT S473 and T308 along with the other 21 AKT-mTOR signaling proteins. In addition, the relationship of phosphorylated protein expression change by treatment from baseline for each of the 23 RPPA biomarkers will be correlated with tumor response by Spearman rank correlation coefficient test.

Blood will be collected for CyTOF analysis. This analysis will focus on immune populations that change with those patients who may have responded to NACT + ipatasertib. We hypothesize that tumors that responded to treatment will have different immune population changes than those tumors that do not respond to treatment.

The purpose of translational research objectives is to explore and possibly generate hypotheses for future study. Therefore there will be no adjustment for multiple tests. Due to small sample size of this study, exact testing procedure, e.g., exact Spearman's rank correlation test, may be used where it is appropriate.

13.10 Gender/Ethnicity/Race Distribution

The expected gender/ethnicity/race distribution is based on patients from the NRG-GY007 who had cell type as serous or endometroid, a phase I/II study of Ruxolitinib with front-line neoadjuvant and post-surgical therapy in patients with advanced ovarian, fallopian tube, or primary peritoneal cancer.

	DOMESTIC PLANNED ENROLLMENT REPORT
	Ethnic Categories

Racial Categories	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1		0		1
Asian	0		0		0
Native Hawaiian or Other Pacific Islander	0		0		0
Black or African American	2		0		2
White	31		2		33
More Than One Race	0		0		0
Total	34		2		36

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

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APPENDIX I – FIGO OVARIAN CANCER STAGING 2014

STAGE I: Tumor confined to ovaries

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

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

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

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

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

STAGE IV: Distant metastasis excluding peritoneal metastasis

- IVA Pleural effusion with positive cytology

IVB Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity).

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions

APPENDIX II – PERFORMANCE STATUS CRITERIA

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

APPENDIX III – NYHA CLASSIFICATION

Congestive Heart Failure – New York Heart Association Classification

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

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

APPENDIX IV - CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in NRG Oncology trials.

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using creatinine clearance (mL/min) from the Cockcroft-Gault formula.

2) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dL.**

3) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles but will be subject to dose modification for toxicity as noted in the protocol.

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

5) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR [or estimated CrCl] + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x actual body Weight* (kg)}}{\textbf{72 x serum creatinine (mg/dl)}} \quad \textbf{\{x 0.85 } \textit{\textbf{if female}}\textbf{\}}$$

Notes:
1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient.
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
   c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**

d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) (+ 45.5 females) or (+ 50 for men)
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

At the time of a dose modification for toxicity:
If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

APPENDIX V – GENERAL THERAPY GUIDELINES

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

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

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

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

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

APPENDIX VI- 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 VII – BIOSPECIMEN COLLECTION AND SUBMISSION MANUAL

The NRG-GY027 Biospecimen Collection and Submission Manual provides essential information regarding:

- Biospecimen(s) submission for correlative studies as described in Section 10 of the NRG-GY027 protocol.

These instructions should be distributed to all staff involved with any aspect of biospecimen collection and submission.

Table of Contents

1. Obtaining an NRG Bank ID for Biospecimens

An NRG Bank ID is automatically assigned once the biospecimen consent questions are completed in Rave. The biospecimen consent questions are located on the Eligibilty Checklist.

All biospecimens and accompanying paperwork must be labeled with this coded patient number. Please contact Support if you need assistance (Email: support@nrgoncology.org).

2. Submitting Biospecimen Transmittal Forms

A biospecimen transmittal form for each biospecimen will be available in the **Translational Research Folder in Rave**, once the biospecimen consent questions have been completed.

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

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

Retain a printout of the completed form in the patient's research record.

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

3. Biospecimen Submission

3.1 Mandatory Biospecimen Submission

The patient agrees to participate in mandatory biospecimen collection as part of the main trial. Participating sites are required to submit the patient's biospecimens as outlined below.

3.1.1 Central Review

Not applicable

3.1.2 Correlative Science

3.1.2.1 Mandatory Biospecimens Shipped to EET Biobank (22-DEC-2023)

Biospecimen Kit(s)	One single-chamber biospecimen kit will be provided per patient for the collection and shipment of all mandatory and optional frozen biospecimens. • Collection tubes for the mandatory whole blood and plasma collection are not provided in the kit. • PROT1 reagent for the optional CyTOF specimens is provided in the kit. Sodium heparin tubes for CyTOF whole blood collection are not provided in the kit.

	Sites can order kits online via the Kit Management system (https://kits.bpc-apps.nchri.org). Each site may order two kit types per protocol per day (daily max = 6 kits). Please contact the EET Biobank if you need assistance (Email: BPCKitManagement@nationwidechildrens.org; Phone: 614-722-2865). Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days. Supplies will not be provided for the collection or shipment of FFPE.
Shipping Address	EET Biobank / Protocol NRG-GY027 Nationwide Children's Hospital 700 Children's Dr, WA1340 Columbus, OH 43205 Phone: 614-722-2865 FAX: 614-722-2897 Email: BPCBank@nationwidechildrens.org
Shipping Costs	Sites are responsible to cover all shipping costs to send specimens to the EET Biobank. FFPE should be shipped in your own container at your own expense.
Questions	EET Biobank / Protocol NRG-GY027 Phone: 614-722-2865 Email: BPCBank@nationwidechildrens.org

3.1.2.1.1 Pre-Treatment Formalin-Fixed, Paraffin-Embedded (FFPE) Tissue

Purpose	**Integrated biomarker:** WES, RNAseq, IHC, RPPA
Required for	All patients
Biospecimen(s)	• Pre-treatment archival FFPE metastatic (preferred) or primary (acceptable) tumor collected from laparoscopy (preferred) or five 18G cores (embedded in one block) by radiology or interventional radiology (acceptable) – Block must be submitted • Interval debulking surgery (IDS) archival FFPE metastatic (preferred) or primary (acceptable) tumor block; if possible, IDS tumor tissue should be collected from the same site as the pre-treatment tumor tissue Submission of tissue is required for all patients. Investigators should check with their site's pathology department regarding release of tissue before approaching patients about participation in the trial.
Collection time point(s) and biospecimen code(s)	Pre-treatment archival FFPE – 1st Choice: Metastatic (FM01) tumor collected prior to all treatment 2nd Choice: Primary (FP01) tumor collected prior to all treatment IDS archival FFPE –

	1st Choice: Metastatic (FM02) tumor collected at IDS 2nd Choice: Primary (FP02) tumor collected at IDS
Biospecimen Labeling	Bank ID (N # # # # # # # # #)* NRG ID (X X # # # - GY027 - # # # # #) Biospecimen code (see above) Collection date (mm/dd/yyyy) Surgical pathology accession number Block number *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.
Biospecimen Processing	Not applicable
Biospecimen Storage at Site	Ambient (room temperature)
Required Documentation	• Biospecimen transmittal • Partially redacted pathology report: Patient identifiers such as name, date of birth, medical record number, social security number, and insurance information must be removed from the pathology report. Date of procedure, Surgical Pathology ID, block number, and diagnosis **must** be left on the report. The report must also be labeled with the NRG Bank ID and Patient ID.
Shipping Instructions	• Biospecimens should not be shipped until after patient registration and Bank ID assignment • Ship using your own container • Do not ship FFPE for Saturday delivery

3.1.2.1.2 Frozen Tissue

Purpose	**Integrated biomarker:** PK
Required for	All patients
Biospecimen(s)	250mg preferred (minimum 100mg) • Interval debulking surgery (IDS) snap-frozen normal tissue • IDS snap-frozen metastatic (preferred) or primary (acceptable) tumor; if possible, IDS tumor tissue should be collected from the same site as the pre-treatment tumor tissue Submission of tissue is required for all patients. Investigators should check with their site's pathology department regarding release of tissue before approaching patients about participation in the trial.
Collection time point(s) and biospecimen code(s)	IDS Normal (RN02) snap-frozen tissue collected at IDS IDS Tumor snap-frozen tissue – 1st Choice: Metastatic (RM02) tumor collected at IDS 2nd Choice: Primary (RP02) tumor collected at IDS
Biospecimen	Bank ID (N # # # # # # # # #)*

Labeling	NRG ID (X X # # # - GY027 - # # # # #) Biospecimen code (see above) Collection date (mm/dd/yyyy) Surgical pathology accession number Block number *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.
Biospecimen Processing	1. Label as many 2mL cryovials as needed for tissue collection and pre-chill either on dry ice or within a -80°C freezer. 2. Place each tissue segment in a pre-chilled, pre-labeled cryovial. Note: Tissue segments should be small enough to move freely within the cryovial. 3. Snap freeze tissue on dry ice or in the vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen). If neither dry ice nor liquid nitrogen is available, slow freeze tissue in a -70°C to -80°C freezer. 4. Immediately store snap frozen tissue in a liquid nitrogen freezer (at vapor phase), tissue in a liquid nitrogen freezer (at vapor phase), a -70°C to -80°C freezer, or by direct exposure with dry ice until ready to ship.
Biospecimen Storage at Site	-70ºC to -80ºC freezer or direct exposure with dry ice. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.
Required Documentation	• Biospecimen transmittal • Partially redacted pathology report: Patient identifiers such as name, date of birth, medical record number, social security number, and insurance information must be removed from the pathology report. Date of procedure, Surgical Pathology ID, block number, and diagnosis **must** be left on the report. The report must be also labeled with the NRG Bank ID and Patient ID.
Shipping Instructions	**For all frozen biospecimens:** 1. Pre-fill the kit chamber about 1/3 full with dry ice. 2. Place each biospecimen type and timepoint in a separate zip-lock bag. 3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 20 cryovials in a single chamber kit. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes. 4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice. 5. Insert a copy of the biospecimen transmittal for each biospecimen. 6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.

	7. Complete a FedEx airbill and attach to the top of the shipping container. 8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.

3.1.2.1.3 Whole Blood

Purpose	**Integrated biomarker:** WES, RNAseq
Required for	All patients
Biospecimen(s)	10mL whole blood drawn into purple top (EDTA) tube(s)
Collection time point(s) and biospecimen code(s)	Baseline (WB01) prior to study treatment
Biospecimen Labeling	Bank ID (N # # # # # # # # #)* NRG ID (X X # # # - GY027 - # # # # #) Biospecimen code (see above) Collection date (mm/dd/yyyy) *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.
Biospecimen Processing	1. Label the purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount. 2. Draw 10mL of blood into the labeled purple top tube(s). 3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA. 4. Ship whole blood the day collected. If the whole blood absolutely cannot be shipped the day collected, the tube(s) should be refrigerated (4°C) and shipped within 24 hours. Do not collect whole blood the day before a holiday.
Biospecimen Storage at Site	If absolutely cannot ship same day, refrigerate (4°C) and ship within 24 hours.
Required Documentation	Biospecimen transmittal
Shipping Instructions	1. Place the whole blood biospecimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag. 2. Wrap the biohazard envelope in bubble wrap or another padded material. 3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope. 4. Place the Tyvek envelope in a sturdy shipping container. 5. Insert a copy of the biospecimen transmittal for each biospecimen. 6. Complete a FedEx airbill and attach to the top of the shipping container. 7. Attach an Exempt Human Specimen sticker to the outside of the shipping container.

3.1.2.1.4 Interval Debulking Surgery Plasma

Purpose	**Integrated biomarker:** PK
Required for	All patients
Biospecimen(s)	Plasma processed from 7-10mL whole blood drawn into purple top (EDTA) tube(s)
Collection time point(s) and biospecimen code(s)	Interval debulking surgery (PB01)
Biospecimen Labeling	Bank ID (N # # # # # # # # #)* NRG ID (X X # # # - GY027 - # # # # #) Biospecimen code (see above) Collection date (mm/dd/yyyy) *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.
Biospecimen Processing	**Plasma should be processed and frozen within two hours of collection; within one hour is ideal.** 1. Label cryovials and 15mL conical tube as described above. Use 2mL cryovials as plasma will be shipped to EET Biobank. 2. Draw 7-10mL of blood into lavender/purple top (EDTA) tube(s). 3. Immediately after collection, gently invert the blood collection tube 5-10 times to mix blood and EDTA. 4. Centrifuge blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate plasma (top, straw-colored layer) from red blood cells (bottom, red layer). 5. Transfer plasma into pre-labeled 15mL conical tube and gently mix. 7. Quickly, evenly dispense (aliquot) plasma into pre-labeled cryovials and cap tubes securely. Place at least 0.25mL into each cryovial. **Avoid any residual cells that pellet at the bottom of the conical tube.** 8. Immediately **freeze plasma in an upright position** in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship.
Biospecimen Storage at Site	-70ºC to -80ºC freezer or direct exposure with dry ice. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.
Required Documentation	Biospecimen transmittal
Shipping Instructions	**For all frozen biospecimens:** 1. Pre-fill the kit chamber about 1/3 full with dry ice. 2. Place each biospecimen type and timepoint in a separate zip-lock bag. 3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 20 cryovials in a single chamber kit. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.

	4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice. 5. Insert a copy of the biospecimen transmittal for each biospecimen. 6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber. 7. Complete a FedEx airbill and attache to the top of the shipping container. 8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.

3.2 Optional Biospecimen Submission

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

3.2.1 Central Review

Not applicable

3.2.2 Correlative Science

3.2.2.1 Optional Biospecimens Shipped EET Biobank (22-DEC-2023)

Biospecimen Kit(s)	One single-chamber biospecimen kit will be provided per patient for the collection and shipment of all mandatory and optional frozen biospecimens. • Collection tubes for the mandatory whole blood and plasma collection are not provided in the kit. • PROT1 reagent for the optional CyTOF specimens is provided in the kit. Sodium heparin tubes for CyTOF whole blood collection are not provided in the kit. Sites can order kits online via the Kit Management system (https://kits.bpc-apps.nchri.org). Each site may order two kit types per protocol per day (daily max = 6 kits). Please contact the EET Biobank if you need assistance (Email: BPCKitManagement@nationwidechildrens.org; Phone: 614-722-2865). Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.
Shipping Instructions	**For all frozen biospecimens:** 1. Pre-fill the kit chamber about 1/3 full with dry ice. 2. Place each timepoint of frozen plasma in a separate zip-lock bag. 3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 20 cryovials in a single

	chamber kit. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes. 4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice. 5. Insert a copy of the biospecimen transmittal for each biospecimen. 6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber. 7. Complete a FedEx airbill and attache to the top of the shipping container. 8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
Shipping Address	EET Biobank / Protocol NRG-GY027 Nationwide Children's Hospital 700 Children's Dr, WA1340 Columbus, OH 43205 Phone: 614-722-2865 FAX: 614-722-2897 Email: BPCBank@nationwidechildrens.org
Shipping Costs	Sites are responsible to cover all shipping costs to send specimens to the EET Biobank. FFPE should be shipped in your own container at your own expense.
Questions	EET Biobank / Protocol NRG-GY027 Phone: 614-722-2865 Email: BPCBank@nationwidechildrens.org

3.2.2.1.1 Frozen Tissue

Purpose	**Integrated biomarker:** PK
Required for	All patients
Biospecimen(s)	250mg preferred (minimum 100mg) • Pre-treatment archival snap-frozen normal tissue • Pre-treatment archival metastatic (preferred) or primary (acceptable) tumor collected from laparoscopy (preferred) or by radiology or interventional radiology (acceptable)
Collection time point(s) and biospecimen code(s)	Pre-treatment archival snap-frozen normal tissue (RN01) Pre-treatment archival snap-frozen tumor – 1st Choice: Metastatic (RM01) tumor collected prior to all treatment 2nd Choice: Primary (RP01) tumor collected prior to all treatment
Biospecimen Labeling	Bank ID (N # # # # # # # # #)* NRG ID (X X # # # - GY027 - # # # # #) Biospecimen code (see above) Collection date (mm/dd/yyyy) Surgical pathology accession number Block number

	*Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.
Biospecimen Processing	1. Label as many 2mL cryovials as needed for tissue collection and pre-chill either on dry ice or within a -80°C freezer. 2. Place each tissue segment in a pre-chilled, pre-labeled cryovial. Note: Tissue segments should be small enough to move freely within the cryovial. 3. Snap freeze tissue on dry ice or in the vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen). If neither dry ice nor liquid nitrogen is available, slow freeze tissue in a -70°C to -80°C freezer. 4. Immediately store snap frozen tissue in a liquid nitrogen freezer (at vapor phase), tissue in a liquid nitrogen freezer (at vapor phase), a -70°C to -80°C freezer, or by direct exposure with dry ice until ready to ship.
Biospecimen Storage at Site	-70°C to -80°C freezer or direct exposure with dry ice. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.
Required Documentation	• Biospecimen transmittal • Partially redacted pathology report: Patient identifiers such as name, date of birth, medical record number, social security number, and insurance information must be removed from the pathology report. Date of procedure, Surgical Pathology ID, block number, and diagnosis **must** be left on the report. The report must also be labeled with the NRG Bank ID and Patient ID.

3.2.2.1.2 CyTOF Whole Blood

Purpose	**Exploratory biomarker:** CyTOF
Optional for	All patients
Biospecimen(s)	5mL whole blood drawn into green top (sodium heparin) tube(s) processed with PROT1
Collection time point(s) and biospecimen code(s)	• Baseline (WB03) prior to study treatment • IDS (WB04) at interval debulking surgery
Biospecimen Labeling	Bank ID (N # # # # # # # # #)* NRG ID (X X # # # - GY027 - # # # # #) Biospecimen code (see above) Collection date (mm/dd/yyyy) *Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10.
Biospecimen Processing	1. Label green top (sodium heparin) collection tube(s), 15mL empty conical tube (provided), and four 5mL Eppendorf tubes (provided) as described below. 2. Draw 5mL of blood into the labeled green top tube(s).

	3. Immediately after collection, gently invert the green top tube 5-10 times to mix the blood and sodium heparin. 4. Transfer the 5mL of heparinized blood to the labeled empty conical tube and add 7mL of PROT1 (provided). **Note: PROT1 is hypotonic; the solution must be added to the blood (rather than the blood added to the solution).** **5.** Secure the conical tube cap and gently invert 10 times to mix the heparinized blood with the PROT1. 6. Allow the heparinized blood/PROT1 mixture to sit at room temperature for 8 minutes. 7. Transfer 2.4mL of the heparinized blood/PROT1 mixture to each of four 5mL Eppindorf tubes. **Note: The blood should be transferred to Eppindorf tubes and frozen before 10 minutes has elapsed.** 8. Immediately transfer the Eppendorf tubes to a -80°C freezer or place in direct contact with dry ice. **Note: It is critical to store at -80°C. Processed samples cannot be stored at temperatures warmer than -80°C.**
Biospecimen Storage at Site	-80°C freezer or place in direct contact with and completely cover in dry ice. **Note: It is critical to store at -80°C. Processed samples cannot be stored at temperatures warmer than -80°C.**
Required Documentation	Biospecimen transmittal

4. Biospecimen Processing and Storage at the EET Biospecimen Bank (22-DEC-2023)

FFPE tissue blocks will be received and stored at room temperature until processed for distribution for analysis. See Section 10.3.2.2 for details on DNA and RNA extractions and storage of nueclic acids.

Germline DNA will be extracted from whole blood collected in EDTA tubes. DNA will be quantitated and stored in a -80°C freezer until distribution for analysis.

Plasma will be stored in a -80°C freezer until distribution for analysis.

CyTOF whole blood will be stored in a -80°C freezer until distribution for analysis.

5. Patient Withdrawal of Permission for Use of Biospecimens

If an enrolled patient chooses to withdraw permission for use of their biospecimen(s), a biospecimen consent withdrawal form must be submitted to the NRG Oncology Statistics and Data Management Center. Any data obtained from the biospecimen(s) distributed prior to submission of the form may be used.

6. Institution-Initiated Request for Return of Formalin-Fixed, Paraffin-Embedded

(FFPE) Materials

An FFPE Return Request must be submitted to the EET Biobank for any institution-initiated request to return FFPE materials. FFPE will be returned to the submitting institution at the institution's expense. Note: The EET Biobank cannot ship to third party institutions/departments.

The EET Biobank may process blocks prior to return as specified in the clinical trial protocol and/or request that blocks are re-submitted to the bank after use at the site

7. Letter to Pathologists

Dear Pathologist,

Your site is a participant in NRG-GY027, "Phase I/IB safety and pharmacodynamic study of neoadjuvant (NACT) carboplatin and paclitaxel with ipatasertib in ovarian cancer (PTMA 100805)."

This study includes NCI-approved integrated biomarkers/secondary objectives. Given the biospecimen requirements for this biomarker testing, **NRG GY027 requires all sites submit FFPE blocks only (i.e., unstained slides will not be accepted).** Per Eligibility Section 3.1.3:

"Pre-treatment archival formalin-fixed, paraffin-embedded tumor block collected from laparoscopy (preferred) or five 18G cores by radiology or interventional radiology (acceptable) must be available for submission."

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

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

If you should have any questions, please do not hesitate to contact Drs. Katherine Fuh (PI) and [redacted]

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

Sincerely,

Katherine Fuh, MD, PhD
[redacted] PhD, MPH

APPENDIX VIII– CORRELATIVE SCIENCE

The following details the biomarker assays summarized in Section 10. Please refer to Section 2 for biomarker background and significance, and Sections 13.8 and 13.9 for biomarker statistical analysis plan.

1. Integral Biomarkers
Not applicable

2. Integrated Biomarkers
Not applicable

3. Exploratory Biomarkers (24-APR-2023)

3.1 pPRAS40 Immunohistochemistry

BRC review required

3.1.1 Description of Assay
Five µm sections will be obtained and stained with H&E for imaging or immunoreacted for pPRAS40. Briefly, the tissue sections baked at 60ºC, dewaxed, and rehydrated through successive alcohols xylene, 100% EtOH, 95% EtOH, 70% EtOH, and ddH2O2). Antigen retrieval will be performed using an antigen unmasking solution (pH6, Citrate-Based) (Vector, H-3300) at 95oC, and the endogenous peroxidase blocked with Bloxall (Vector, SP-6000). After washing in TBST (Santa Cruz, sc-36231-1). Antigens will be unmasked using a pH9, Tris-based solution (Vector, H-3301), in a Biocare decloaking chamber™ NxGen) (after pressurizing). The slides will be allowed to reach room temperature, washed extensively with ddH2O2 and TBST, and blocked with 3% donkey serum in TBST. The tissues will be then successively incubated with Phospho-PRAS40 (Thr246) (D4D2) XP® Rabbit mAb (RmAb; Cell Signaling; # 13175), anti-Rabbit HRP Polymer (Cell IDX, 2RH-015), washed in TBST, and developed with a brown chromogen (VWR, 95041-478). After 2X washes in ddH2O2, the tissues will be counterstained with Mayer's Hematoxylin (Sigma, 51275-500ml), dehydrated and mounted with a xylene-based mounting medium.

3.1.2 Analytical Performance of Assay
All slides will be scanned using Aperio-Leica AT2 Digital Whole Slide Scanner (https://www.leicabiosystems.com/digital-pathology/scan/aperio-at2/) to generate full-slide digital images in the proprietary svs file format. This format is compatible with the image analysis software to be used. The scanned images will be quantified using the QuPath open-source application (https://doi.org/10.1038/s41598-017-17204-5). Region of interest (ROIs) are selected by using brush or polygon tools. If the sample contains 80% or more tumor cells, a full image annotation will be created. The QuPath positive cell detection (PCD) algorithm will be used to analyze the selected areas. This will generate a table with the number of positive event and the staining intensity.

The results of the immunohistochemistry quantification are reported as H-scores (Goulding H et al, Path. 26:291-294; 1995). The score is given as the sum of the percentage of staining multiplied by an ordinal value corresponding to the intensity level (0 = none, 1 = weak, 2 = moderate, 3 = strong). With these 4 intensity levels, the resulting score ranged from 0 (no staining in the tumor) to 300 (diffuse intense staining of the tumor). If there is significant immunoreactivity in stromal cells, the process will be repeated for the stroma, in this case using exclusively the brush or polygon tools. H-scores are exclusively evaluated for epithelial tumor cells; stromal positive cells are only reported as # of events per area. In each case, the paired T test method will be used to compare pre- and post-treatment values using GraphPad Prism version 7.00 for Windows (GraphPad Software, La Jolla California).

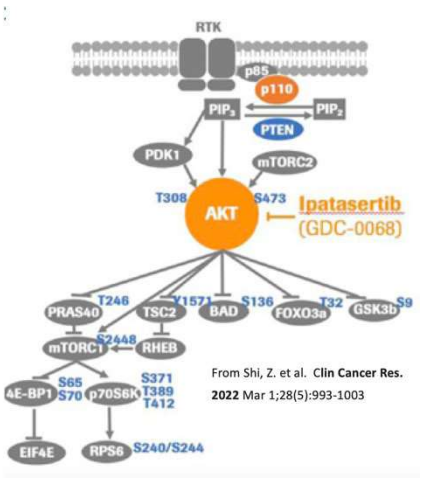
3.2 AKT-mTOR Signaling Pathway (24-APR-2023)

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

3.2.1 Description of Assay (24-APR-2023)

The assay is an antibody-based reverse phase protein array (RPPA) that semi-quantitatively measures the abundance of phosphorylated proteins and total proteins in cell lysates derived from cell culture, whole tissue, cellular isolates, microdissected cells, serum, or body fluids in a direct deposition micro dot-blot configuration.

The following 23 members of the AKT-mTOR protein signaling pathway will be quantitatively measured by LCM-RPPA based analysis of the pre-treatment baseline FFPE tissue samples.



PTEN (S380)
PTEN
PDK1 (S241)
Akt (T308)
Akt (S473)
FKHR/FOX01 (S256)
FKHR-FOX01 (T24)/FKHRL1-FOX03a (T32)
PRAS40 (T246)
Tuberin/TSC2 (Y1571)
SGK1 S78
GSK-3alpha/beta (S21/9)
mTOR (S2448)
mTOR (S2481)
eIF4E (S209)
eIF4G (S1108)
p70 S6 Kinase (S371)

p70 S6 Kinase (T389)
p70 S6 Kinase (T412)
S6 Ribosomal Protein (S235/236)
S6 Ribosomal Protein (S240/244)
4E-BP1 (T37/46)
4EBP1 (S65)
4EBP1 (T70)

All testing will be performed at the RPPA laboratories in the CLIA/CAP accredited George Mason University Center for Applied Proteomics and Molecular Medicine (CAPMM; CLIA #49D2002076, CAP #7223012).

Briefly, tumor cells are isolated from slides by laser microdissection (LMD). The tumor cells are lysed and proteins are extracted in a SDS-based chemical detergent. The protein extracts are printed onto nitrocellulose slides by automated arrayer. The arrayed slides are incubated with validated primary and secondary antibodies Stained slides are scanned by a fluorescence slide scanner and spot intensity values are determined. Spot intensities for protein analyte slides are compared to a total protein normalization spot in order to facilitate data analysis. A normalized intensity value is used for correlative analysis.

Analytical Performance of Assay (24-APR-2023)

For tumor-based clinical and pre-clinical applications, RPPA coupled to LMD can provide a powerful workflow to study the tumor microenvironment whereby hundreds of protein and phosphoproteins can be measured and quantified at once in LMD enriched tumor epithelium and stroma and immune cell populations both proximal and distal to the invading epithelium. These populations are lysed and printed onto slides using an automated arrayer in a CLIA validated workflow that requires only a few nanoliter volume of lysate per slide with less than 2µg total protein needed to measure ~400 analytes.

For immunohistochemistry (IHC), single antibodies directed against an epitope of interest are used to quantify the presence of proteins for an individual slide. The RPPA technology, which using many of the same primary antibodies as those used in IHC, can measure of hundreds of signaling proteins concomitantly from only a few thousand cells, facilitating targeted phospho-proteomic analysis with 10-1000 fold less input material than mass spectrometry or IHC. [1-6]

Previous studies by us and others have also revealed the absolute requirement for upfront histologically-guided microdissection-based cellular enrichment in order to produce clinically accurate information about drug target activation levels in individual patient tumor samples for clinical decision making.[7,8] Thus, RPPA provides a critical means of broad-scale cell signaling analysis directly from tissue samples that other existing technologies cannot achieve.

Using the RPPA technology, serial dilutions of each sample are printed along with known high and low controls, calibration curves from contrived ad-mixtures of cell lysates containing known amounts of each analyte, to maintain sample concentration. Each spot contains a bait zone measuring only a few hundred microns in diameter. The detection probe can be tagged and

signal amplified independently from the immobilized analyte protein. Coupling the detection antibody with highly sensitive amplification systems can yield detection sensitivities to fewer than 1,000 to 5,000 molecules per spot with good linearity (correlation coefficient or R^2 = 0.990-0.999) and inter-experiment precision (R^2= 0.973). Between run and within run analytical precision is between a 3-13% CV (coefficient of variation).[9]

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APPENDIX IX- PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD
Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

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

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

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

	Explanation
CYP isoenzymes	The enzyme in question is CYP3A4. Ipatasertib is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. Ipatasertib is an inhibitor of CYP3A4 and may affect the metabolism of other drugs.

These are the things that you need to know:
The study drug, ipatasertib, may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.
Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inhibitors or inducers of CYP3A4 or sensitive substrates of CYP3A4."

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
    - Avoid ingestion of grapefruit, grapefruit juice or grapefruit supplements.
- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version *JUN/2020*

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTIT EMERGENCY INFORMATION	NIH NATIONAL CANCER INSTIT	NIH NATIONAL CANCER INSTIT DRUG INTERACTIONS	NIH NATIONAL CANCER INSTIT
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Ipatasertib interacts with CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme. Ipatasertib is an inhibitor of CYP3A4 and may affect the metabolism of other drugs and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** Ipatasertib	**Use caution and avoid the following drugs if possible:** Avoid ingestion of grapefruit, grapefruit juice or grapefruit supplements.	Your healthcare providers should be aware of any medicines that are "strong inhibitors or inducers of CYP3A4 or sensitive substrates of CYP3A4." **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version JUN/2020	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov

Fold at dotted lines:

APPENDIX X- PATIENT DRUG DIARIES

IPATASERTIB

Today's Date _____ Cycle # _____

Patient Name Patient Study ID

Complete one form for each cycle (21 days).

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

IPATASERTIB

Take **(number)** mg tablets once a day. Ipatasertib may be taken with or without food. Each dose of ipatasertib should be taken with a minimum of 3 ounces (90 mL) of fluid.

Day	Date	100mg	200mg	AM
Example	*1/1/22*	*1*	*1*	*7:00*
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature Date