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DEPARTMENT OF MEDICAL ONCOLOGY

TITLE: A Phase I/IB Study of Ipatasertib in Combination with Carboplatin, Carboplatin/Paclitaxel, or Capecitabine/Atezolizumab in Patients with Metastatic Triple Negative Breast Cancer

CITY OF HOPE PROTOCOL NUMBER: IRB #18496 **PROTOCOL DATED: 02/10/2023**

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SITE: Breast Cancer
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Clinical Trial Protocol

TITLE:	A Phase I/IB Study of Ipatasertib in Combination with Carboplatin, Carboplatin/Paclitaxel, or Capecitabine/Atezolizumab in Patients with Metastatic Triple Negative Breast Cancer
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INDICATION:	Metastatic Triple Negative Breast Cancer
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SUPPORT PROVIDED BY:	Genentech, Inc. City of Hope National Cancer Center
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Protocol Synopsis

Protocol Title
A Phase I/IB Study of Ipatasertib in Combination with Carboplatin, Carboplatin/Paclitaxel, or Capecitabine/Atezolizumab in Patients with Metastatic Triple Negative Breast Cancer
Brief Protocol Title for the Lay Public (if applicable)
Ipatasertib plus carboplatin,carboplatin/paclitaxel, or Capecitabine/Atezolizumab in triple negative breast cancer
Study Phase
Phase I/IB
Participating Sites
City of Hope Comprehensive Cancer Center
Rationale for this Study
Triple-negative breast cancer (TNBC) is a heterogeneous disease with limited treatment options and very poor prognosis for metastatic disease, with median progression-free survival with chemotherapy ranging from 2.5 to 4 months. In addition, there is limited effective targeted therapy in patients with metastatic TNBC with the exception of tumors with germline BRCA mutation, which highlights TNBC as an area of unmet need. The Cancer Genome Atlas (TCGA) analysis demonstrated that the most frequent loss-of-function and gain-of-function alterations in TNBC involve genes associated with DNA damage repair and phosphatidylinositol 3-kinase (PI3K) signaling pathway, including the axis of PI3K-mTOR-Akt /PTEN loss. Non-basal subtypes (i.e. LAR, M and MSL) demonstrated relatively high PIK3CA –activating mutations and exhibit sensitivity to PI3K inhibitors *in vitro*. In addition, the mTOR inhibitor everolimus has shown activity in basal-like TNBC. Nevertheless, use of PI3K inhibitors as single agent therapy has proven minimally effective secondary to multiple feedback mechanisms. Combination therapies with chemotherapy agents have shown synergy, and we are conducting a phase I/IB study combining eribulin with everolimus in metastatic TNBC as one such strategy (NCT02120469). Another strategy utilizing this pathway revolves around AKT. Ipatasertib (GDC-0068) is a novel selective ATP-competitive small-molecule inhibitor of AKT that preferentially targets active phosphorylated Akt (pAkt) and is potent in cell lines with evidence of Akt activation. Ipatasertib displays synergy when combined with taxanes or other chemotherapeutic agents (Gemcitabine, platinum, 5-FU, doxorubicin(1), paclitaxel) *in vitro*. In a phase I study, ipatasertib was well-tolerated with a maximum tolerated dose (MTD) of 600 mg daily dosed 21 days on and 7 days off. The most common adverse events were grade 1–2 diarrhea, nausea, asthenia, and hyperglycemia. In the Phase Ib study, ipatasertib combined with docetaxel or mFOLFOX6, was well-tolerated with evidence of anti-tumor activity and MTD of 600mg daily. Currently, the combination of paclitaxel (80mg/m2, days 1, 8,15 every 4 weeks) and ipatasertib (400mg daily 3 weeks on and 1 week off) are being studied in both the metastatic setting (NCT02162719) and the neoadjuvant setting (NCT02301988) in TNBC. In the LOTUS trial, combination of paclitaxel 80mg/m2 (days 1, 8 & 15) and ipatasertib 400mg po days 1-21 every 28 days has shown modestly-improved PFS. The combination regimen was well-tolerated with 23% of grade ≥3 diarrhea and 18% grade 3

neutropenia.

The combination of ipatasertib with single DNA-damaging agents is another potential strategy for synergy. DNA-damaging agents such as platinum drugs (cisplatin and carboplatin) are active in TNBC. In the randomized TNT trial, single-agent carboplatin was compared to single-agent docetaxel in patients with metastatic TNBC. Patients with TNBC and germline *BRCA 1/2* mutations were found to have a higher response rate and longer progression-free survival rates favoring carboplatin over docetaxel. Weekly paclitaxel (100mg/m2) was combined with weekly carboplatin AUC 2, days 1, 8, and 15 on a 4 week schedule in a cohort of advanced breast cancer patients. The regimen was effective with a response rate of 62% and was well tolerated with a grade 3/4 neutropenia rate of 35%. Other grade 3/4 toxicities included neuropathy (11%), infection (6%), weakness (6%), anemia (5%), and paresthesia (3%). This study showed that weekly carboplatin/ paclitaxel produces response rates comparable with those seen with the q3w schedule, but with a more favorable toxicity profile. A high proportion of TNBC tumors exhibit BRCAness-like status, which indicate these tumors are highly sensitive to platinum salts.

In the patient-derived xenograft model of mTNBC, carboplatin and ipatasertib were synergistic in tumor suppression (unpublished data). Based on this evidence, we hypothesize that carboplatin or carboplatin/paclitaxel plus the Akt inhibitor ipatasertib will have a synergistic effect in TNBC. Hence arms (A and B) of this clinical trial are designed to determine the dose and safety of the doublet ipatasertib/carboplatin and triplet combination ipatasertib/carboplatin/paclitaxel and obtain initial evidence of efficacy.

The Impassion130 study demonstrated the addition of atezolizumab (anti-PD-L1) to nab-paclitaxel improved PFS and OS outcomes in PD-L1 positive mTNBC in the first line setting. It remains unknown whether non-taxane chemo + anti-PD-1/L1 will be beneficial in mTNBC. CREATE-X study that supports the use of adjuvant capecitabine for patients who have residual disease after standard neoadjuvant chemotherapy. Given these data, as well as promising data supporting the use of immune checkpoint inhibition (ICI) in TNBC, there is a strong interest in testing the combination of an ICI in combination with capecitabine. In a phase IB study, the combination of ipatasertib, atezolizumab and paclitaxel or nab-paclitaxel showed a promising response rate of 73% in a cohort of 26 patients with unresectable, locally advanced/metastatic TNBCs previously untreated in the metastatic setting. Interestingly, responses were high irrespective of PD-L1 status or PI3K/AKT/PTEN alteration status(2).In the third arm of this study, arm C, we aim to test the combination of ipatasertib, capecitabine and atezolizumab in patients with mTNBC.

As a result, in the current trial, we will study the following combinations in patients with metastatic TNBCs: carboplatin+ ipatasertib, carboplatin + paclitaxel + ipatasertib, capecitabine + atezolizumab + ipatasertib. The primary objective is to determine the recommended starting dose for each combination, further evaluate the safety of the combinations and obtain initial evidence of activity . In addition, blood and tumor samples are collected for correlative analysis in order to identify potential biomarkers associated with response to therapy.

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Objectives

Primary Objective

- To determine the recommended Phase II dose of ipatasertib plus carboplatin (arm A), ipatasertib plus carboplatin/paclitaxel (arm B), or ipatasertib, atezolizumab, and capecitabine (arm C) in patients with metastatic TNBC

Secondary Objectives

- To obtain initial evidence of activity by examining progression-free survival of each dose regimen
- To confirm the RP2D safety in expanded cohort by evaluating toxicities and confirm tolerability of the combinations
- To obtain evidence of activity by examining response rate based on RECIST 1.1.
- To evaluate clinical benefit rate (CBR), event-free survival, time-to-treatment failure and overall survival
- To further describe the cumulative toxicities (CTCAE 5.0) of the combinations
- To evaluate patient's quality of life (QOL)

Exploratory Objectives

- To evaluate the progression-free survival and overall survival, based on the genomic alterations including *PIK3CA/AKT/PTEN* alterations and BRCA status
- To study the association of TNBC mRNA expression profiling including Vanderbilt molecular subtype and treatment response
- To study the association of stool microbiome and calprotectin with diarrhea
- To study peripheral blood circulating tumor DNA (ctDNA)
- To study therapy resistance by analyzing tumor genomics and transcriptome analysis
- To study the profiles of peripheral blood mononuclear cells and its association with response to therapy
- To study tumor immune biomarkers and its association with response

Study Design:

Endpoints

Primary Endpoint

Phase I:

- To determine the recommended Phase II dose of ipatasertib plus carboplatin (arm A), ipatasertib plus carboplatin/paclitaxel (arm B), and ipatasertib, atezolizumab, and capecitabine (arm C)

Phase IB:

- Progression Free Survival

Secondary Endpoint

- Response Rate by RECIST 1.1
- Clinical Benefit Rate
- Event-free Survival
- Time-to-treatment Failure
- Overall Survival
- Toxicities by CTCAE 5.0

Sample Size

Arm A and B: Minimum 28 evaluable: Maximum 40 evaluable patients; Expect 28 patients evaluable for DLT considerations. Assuming a 20% inevaluable rate, expected sample-size is 34 patients starting treatment.

Arm C: We expect 17-18 patients for dose-finding with interquartile range of 15-20 patients. Additional patients will be added at the RP2D to have at least 12 patients treated at the RP2D.With 12 patients at the RP2D, any specific severe toxicity with 20% incidence will be observed with 93% probability.

Estimated Duration of the Study

The trial will require approximately 36 months for accrual, approximately 12 months of minimum follow-up to assess response, and continued follow-up for 36 months to assess PFS and OS, and to evaluate toxicities.

Summary of Subject Eligibility Criteria

Inclusion Criteria

- Men or women age ≥ 18 years
- ECOG PS 0-1
- Histologically or cytologically confirmed triple negative breast cancer defined by ER or PR ≤10% by IHC and HER2 negative
- RECIST 1.1 measurable disease (Arm C only; RECIST non-measurable disease allowed for Arm A and B)
- 0- 2 lines of chemotherapy and/or biological targeted therapy in the metastatic setting
- Mandatory baseline archival tissue available for determination of PI3K/AKT/PTEN status
- Life expectancy ≥ 3 months
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
    - ANC $\geq 1.5 \times 10^9$/L (1500/μL) without granulocyte colony-stimulating factor support

- Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
- Hemoglobin ≥ 90 g/L (9 g/dL) (Patients may be transfused to meet this criterion.)

– Adequate liver function defined by:
- AST and ALT $\leq 2.5 \times$ ULN, with the following exception:
- Patients with documented liver metastases may have AST and ALT $\leq 5 \times$ ULN.
- ALP $\leq 2 \times$ ULN, with the following exceptions:
- Patients with known liver involvement may have ALP $\leq 5 \times$ ULN
- Patients with known bone involvement may have ALP $\leq 7 \times$ UL
- Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN

– Adequate renal function defined by: Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50mL/min (calculated using the Cockcroft-Gault formula)

– PTT (or aPTT) and INR $\leq 1.5 \times$ ULN

– Fasting total glucose ≤ 150 mg/dL

– Women of childbearing potential must have a negative serum pregnancy test result within 96 hours prior to initiation of study drug.

– Male patient must use an adequate method of contraception with the first dose of study therapy through 120 days after the last dose of study therapy.

Exclusion Criteria

- ⩾ Grade 3 toxicities from previous treatment, not recovered to ⩽ Grade 2 at study entry
- Prior exposure to PI3K/AKT/mTOR pathway inhibitors including but not limited to everolimus, ipatasertib, gedatolisib or alpelisib etc.
- Prior exposure to carboplatin for treatment of metastatic TNBC not allowed; prior treatment of carboplatin as neoadjuvant or adjuvant therapy allowed if last dose of therapy completed ⩾ 12 months prior to initiation of the current study
- Prior exposure to paclitaxel or nab-paclitaxel for treatment of metastatic TNBC not allowed for Carboplatin/paclitaxel arm; prior treatment of paclitaxel or nab-paclitaxel as neoadjuvant or adjuvant therapy allowed if last dose of therapy completed ⩾ 12 months prior to initiation of the current study
- Prior exposure to capecitabine for treatment of metastatic TNBC not allowed for Arm C; prior treatment of capecitabine as adjuvant therapy allowed if the last dose of therapy completed ⩾ 12 months prior to initiation of the current study for Arm C
- Prior treatment with immune check point inhibitors for Arm C

- Active autoimmune disorders requiring steroid dose higher than prednisone 10mg daily for Arm C
- Active disease or treatment hepatitis B or C or HIV infection for Arm C
- Receipt of a live, attenuated vaccine within 4 weeks prior to start of treatment, during treatment, or within 5 months following the last dose of atezolizumab for Arm C
- Known dihydropyrimidine dehydrogenase (DPD) deficiency in patients selected to receive capecitabine for Arm C
- Known allergy or hypersensitivity to any component of carboplatin and/or paclitaxel or nab-paclitaxel, or capecitabine (5-FU) formulation (unless the patient is being considered for arm lacking the hypersensitivity agent(s)).
- Known severe allergic reactions to cisplatin or other platinum-containing compounds or mannitol (unless enrolling for Arm C)
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Active infection requiring systemic anti-microbial treatment (including antibiotics, anti-fungals, and anti-viral agents)
- Known untreated or unstable brain metastasis or leptomeningeal metastasis from metastatic breast cancer
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 (C1D1) or anticipation of need for a major surgical procedure during the course of the study
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the last dose of ipatasertib and within 6 months after the last dose of paclitaxel, whichever occurs later
- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction $<50\%$; or active ventricular arrhythmia requiring medication
- Current unstable angina or history of myocardial infarction within 6 months prior to C1D1
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) >480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Treatment with approved or investigational cancer therapy within 14 days prior to C1D1

- Patients with a prior diagnosis of malignancy except non-melanomatous skin cancer treated ⩾ 5 years ago are eligible, provided that they have not received prior taxanes or carboplatin as part of their prior treatment regimen, and that they meet all eligibility criteria.

Investigational Product Dosage and Administration

Arm A and B:
Ipatasertib will be given at a starting dose of 400mg oral daily for 28 days.

Carboplatin will be given at a starting dose of AUC 2 on days 1, 8, 15 every 28 days for Triplet Schedule A. Paclitaxel will be given at a dose of 80 mg/m2 administered by IV infusion on days 1,8,15 of every 28 day cycles for Triplet Arm A.

Carboplatin will be given at a starting dose of AUC 2 on days 1, 8, 15 every 28 days for doublet Arm B.

Arm C:
Ipatasertib will be given at a starting dose of 300 mg oral daily for 21 days on 7 days off, every 28 days.Capecitibine will be given at a starting dose of 750 mg/m2, 1 week on 1 week off x 2.
Atezolizumab will be given at a starting dose of 840 mg IV d 1 and 15. Every 28 days is a cycle.

Clinical Observations and Tests to be Performed

Patients who fulfill the eligibility criteria will undergo the full informed consent process. Prior to starting treatment, all subjects will undergo history and physical exam, and laboratory studies including CBC, diff, chemistry, liver function tests, INR/PTT, and viral serology.

Baseline disease will be documented with brain MRI with contrast, bone scan and CT scan of chest, abdomen and pelvis, or PET-CT as long as there is a diagnostic CT component (within 35 days prior to starting treatment).

All subjects will have cardiac function evaluation (within 30 days prior to starting treatment) using an EKG.

CBC with differential and comprehensive serum chemistry panel will be performed on Day 1, 8, 15 of each 4-week cycle and on chemotherapy infusion days through the duration of the study. The study team will monitor the CBCs for dose limiting toxicities (DLTs) evaluation during the first 4 weeks of the study.

Restaging imaging (CT, bone scan if indicated) will be repeated every 12 weeks (+/- 7days). At screening, staging imaging within 35 days (5 weeks) of study entry is allowed. Reading and comparison of two prior staging imaging (3 month and 6 month prior to study entry) are required to document SD per RECIST version 1.1.

During screening, brain imaging will be performed in subjects with known untreated or unstable brain metastases (such subjects also need records of brain imaging performed within the last 3 months prior to screening to establish stability).

Tumor biopsies will be obtained prior to study initiation, at Cycle 2 day 1 (C2D1) and at end of study. If fresh tumor biopsy is not feasible at study entry, archived formalin-fixated paraffin-embedded tumor tissue procured within 6 months of study entry must be obtained. At least 20 x 5um cut of unstained slides with adequate tumor volume must be submitted to study team at time of patient registration. When a core needle biopsy is used, a minimum of 4 core biopsy samples with a minimum 18 gauge needle is required.

Peripheral blood samples will be obtained at baseline (Day 1 cycle 1, D1C1), as well as Day 1 of cycles 2, 4 and end-of-treatment visit. Three tubes (1 x 10 ml green-top, 1 x 10 ml Streck tube (Cell-free DNA BCT®) and 1 x 10 ml lavender-top) of blood will be collected and delivered to the correlative study PI's laboratory. Peripheral blood or biopsy sample can be taken at end of treatment if patient was off trial due to reasons other than disease progression.

Stool sample will be collected at baseline, C4D1 and end-of-treatment visit for microbiome and calprotectin analysis.

Patient reported outcome measured by EORTC QLQ-C30 questionnaire will be completed by patient on C1D1, then every 3 month at the tumor assessment visit, and up to 3 and 6 months after radiological disease progression. The questionnaire should be completed before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment.

Statistical Considerations

Statistical Design for Arm A and B: This is a Phase I trial of ipatasertib plus either carboplatin or carboplatin/ paclitaxel in patients with metastatic TNBC.

Phase: I/IB
Purpose: Safety and Initial Evidence of Efficacy

The combination of paclitaxel and ipatasertib have been well-tolerated and the recommended phase II dose is ipatasertib 400mg po daily 3 weeks on/1 week off, paclitaxel 80mg/m2 days 1, 8,15 of every 4 week cycle. Two dosing regimens will be tested in this study. In triplet schedule A, carboplatin AUC 2, paclitaxel 80mg/m2 will be added on day 1, 8 and 15 of every 4 weeks cycle while patients receive ipatasertib of 400mg daily. In doublet schedule B, carboplatin AUC2 on days 1, 8, 15 every 28 days will be added to ipatasertib 400mg daily continuous dosing.

Primary Objective:

To determine the recommended Phase II dose of ipatasertib plus either carboplatin or carboplatin/paclitaxel in patients with metastatic TNBC

Secondary Objectives:

1. To confirm the recommended Phase II dose safety in an expanded cohort.
2. To evaluate progression-free survival, overall survival and response.
3. Further describe the cumulative toxicities of the combinations
4. To evaluate patient's quality of life (QOL)

Exploratory Objectives:
Preliminary data suggests a better response to ipatasertib in patients with PTEN loss/ PIK3CA-Akt mutated breast tumors. TNBC sub-typing will be performed through mRNA profiling. DNA exome-sequencing via NGS will be used for detecting genomic alterations. These genomic alterations will be associated with clinical responses. The frequency and role of PTEN loss, PIK3CA-Akt pathway status, and BRCA mutation status will be tested as correlatives. The association of stool microbiome and calprotectin with diarrhea will also be studied.

Phase I/Ib Design:
We will use the Phase I Queue (IQ) 3+3 design that ensures patient risk does not exceed the maximum risk permitted in the traditional 3+3 design, while enabling fewer study holds and permits the PI to proceed with a more rapid completion of the Phase I study. A variety of 3-at-risk designs have been conducted, including NCI/CTEP studies based on the 3+3 risk constraints (NCT02568553*,* NCT01567709). This method has been shown (JSM 2016) to reduce study duration by an average of approximately 23% for a typical Phase I study, with a median increase in the number of patients of 1-4, while reducing the number of patients turned away due to lack of slots. The details of the design are described in **section 3**. (see Phase I Queue (IQ) 3+3 table which also has a side-by-side comparison with the classic 3+3 design).

To confirm the recommended Phase II dose obtained from the dose escalation, and for an initial assessment of response, correlatives and PFS estimates, we will enroll an additional cohort of patients until the number treated and evaluable for DLT considerations at the recommended phase II dose is 14 patients for the doublet (Arm B) and for the triplet Arm (Arm A)

All eligible patients who start treatment at the recommended Phase II dose will be considered in the calculation of the response rate.

Sample size for Arm A and B: Expected sample size (if level 1 is well-tolerated) is 14 patients for both the doublet and triplet, for an expected total sample-size of 28 patients. Additional cohorts of 6-8 patients will be required if lower doses are necessary (e.g. level 1 is not well-tolerated) for each Arm.

Statistical Design for Arm C:
Clinical Statistics: For the safety-lead in, a 3 at risk design will be utilized to assess toxicity for the combination therapy as per Table C in Protocol 18496. The DLT period is 1-cycle (28 days).

Each participant will remain on the dosing level according to the escalation dose level they were enrolled in, and intra-dose level escalations will not be allowed, even if the MTD is defined at a higher dose level. Rules for escalation are given in Table C. If a patient comes off study in the first 28 days for any reason outside of toxicity (unrelated

AE, withdrawal of consent, progression of disease etc), this patient will not be considered as evaluable for DLT and this patient should be replaced.

When a maximum tolerable dose level has been defined by the dose escalation portion of the study, and the recommended phase 2 dose (RP2D not to exceed the MTD) has been selected, additional patients will be accrued to confirm the tolerability of the regimen. Specifically, at least 12 patients will be treated at the RP2D to confirm tolerability. Additional patients (beyond the 12 at the RP2D can be accrued if the total number of patients accrued does not exceed 21 patients With 12 patients, any specific severe toxicity with 20% incidence will be observed with 93% probability.

Secondary Objectives: Clinical activity will be described based on the secondary objectives, with a description of the activity based on PD-L1 status. Survival endpoints will be evaluated using Kaplan-Meier methods. Other correlative studies are considered exploratory in the context of this limited Phase I study; however, when the sample size is 12, a single group t-test with a 0.050 one-sided significance level will have 80% power to detect an effect size of 0.766.

Sponsor/Licensee:

City of Hope National Cancer Center.

Note: Genentech is providing Ipatasertib (study drug)

Case Report Forms:

Electronic Data Collection will be used for this protocol. The data will be stored in encrypted, password protected, secure computers that meet all HIPAA requirements.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	*Definition*
ASCO	*American Society of Clinical Oncology*
BRCA	*breast and ovarian cancer susceptibility gene*
CAP	*College of American Pathologists*
CFDA	*China Food and Drug Administration*
CR	*complete response*
CT	*computed tomography*
CTCAE	*Common Terminology Criteria for Adverse Events*
ctDNA	*circulating tumor DNA*
DOR	*duration of response*
EC	*Ethics Committee*
eCRF	*electronic Case Report Form*
EDC	*electronic data capture*
EORTC QLQ-C30	*European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30*
ER	*estrogen receptor*
ESMO	*European Society for Medical Oncology*
FDA	*Food and Drug Administration*
FFPE	*formalin fixed, paraffin embedded*
FNA	*fine-needle aspiration*
GHS	*global health status*
HBcAg	*hepatitis B core antigen*
HBsAg	*hepatitis B surface antigen*
HBV	*hepatitis B virus*
HCV	*hepatitis C virus*
HER2	*human epidermal growth factor receptor 2*
HIPAA	*Health Insurance Portability and Accountability Act*
HR	*hormone receptor*
HRQoL	*health-related quality of life*
iDCC	*independent Data Coordinating Center*
iDMC	*independent Data Monitoring Committee*
ICH	*International Council for Harmonization*

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Abbreviation	*Definition*
IMP	*investigational medicinal product*
IND	*Investigational New Drug (application)*
IRB	*Institutional Review Board*
ITT	*intent-to-treat*
LOH	*loss of heterozygosity*
MRI	*magnetic resonance imaging*
NCI CTCAE	*National Cancer Institute Common Terminology Criteria for Adverse Events*
NGS	*next-generation sequencing*
ORR	*objective response rate*
OS	*overall survival*
PCR	*polymerase chain reaction*
PFS	*progression-free survival*
PgR	*progesterone receptor*
PI3K	*phosphoinositide 3-kinase*
PIK3CA	*phosphatidylinositol-4, 5–bisphosphate 3-kinase, catalytic subunit, alpha*
PK	*Pharmacokinetic*
popPK	*population pharmacokinetics*
PR	*partial response*
PRO	*patient-reported outcome*
PRO-CTCAE	*Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events*
PTEN	*phosphatase and tensin homolog*
QD	*once a day*
QoL	*quality of life*
QTcF	*QT interval corrected using Fridericia's formula*
RBR	*Research Biosample Repository*
RECIST	*Response Evaluation Criteria in Solid Tumors*
SAP	*Statistical Analysis Plan*
TNBC	*triple-negative breast cancer*
ULN	*upper limit of normal*
WES	*whole exome sequencing*
WGS	*whole genome sequencing*

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1. BACKGROUND

1.1 BACKGROUND ON TRIPLE-NEGATIVE BREAST CANCER

Globally, breast cancer is the second most common invasive malignancy and the most common cause of cancer-related mortality in women, with a 5-year survival rate following metastatic diagnosis of approximately 15% (Jemal *et al.* 2011; Ferlay *et al.* 2015).

Triple-negative breast cancer (TNBC) accounts for approximately 20% of all breast cancers and is defined by the absence of immunostaining (<1%) for estrogen receptor (ER), progesterone receptor (PgR), and non-amplified human epidermal growth factor receptor 2 (HER2) expression per American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) guidelines (ASCO/CAP 2010, 2013). Patients with metastatic TNBC exhibit a particularly poor clinical outcome, generally with rapid progression and a median overall survival (OS) rate of approximately 16 months (Rodler *et al.* 2010; Miles *et al*. 2013). Although TNBC may respond to chemotherapy, including taxanes, there are no approved first-line targeted therapies for patients with this specific subtype of breast cancer. Because of an increase in toxicity and little survival benefit with combination chemotherapy, treatment with sequential single agents is generally preferred (Cardoso *et al.* 2017; NCCN 2017). Paclitaxel is considered an appropriate first-line regimen, with a median progression-free survival (PFS) of approximately 6 months in patients with TNBC (Miles *et al.* 2013; Miles *et al.* 2017). There is a pressing need for clinically active agents for the triple-negative subtype of metastatic breast cancer.

PI3K/Akt Pathway in Breast Cancer

The phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway is more frequently activated by genomic aberrations than any other signaling pathway in cancer (LoRusso 2016). The most common genetic alterations in this pathway are activating mutations of phosphatidylinositol-4, 5–bisphosphate 3-kinase, catalytic subunit, alpha (*PIK3CA*), loss-of-function alterations of the tumor suppressor phosphatase and tensin homolog (*PTEN*), deregulation of receptor tyrosine kinase signaling, and amplification and mutations of receptor tyrosine kinases (Cancer Genome Atlas Network 2012; Millis *et al*. 2015). Alterations in Akt itself, including amplification and overexpression of individual Akt isoforms, as well as activating mutations in Akt, have been identified in a subset of human cancers (Bellacosa *et al.* 2005; Brugge *et al.* 2007; Tokunaga *et al.* 2008). All of these mechanisms of pathway activation ultimately funnel through Akt as the central node that drives cell survival, growth, proliferation, angiogenesis, metabolism, and migration (Manning and Cantley 2007).

Large-scale comprehensive genomic analyses have characterized the heterogeneous nature of TNBC, including a subgroup with a PI3K/Akt pathway activation signature characterized by *PIK3CA* or *AKT1* activating mutations and *PTEN* alterations (Cancer Genome Atlas Network 2012). Overall, *PIK3CA*/*AKT1*/*PTEN*-altered tumors are

frequently observed in breast cancer, and are reported in approximately 35% of patients with TNBC and in approximately 50% of HR+/HER2− breast cancers (Cancer Genome Atlas Network, 2012).

To date, the relationship between PI3K/Akt pathway activation and prognosis in early breast cancer is mixed, with some data demonstrating association with favorable outcomes, some data with poor prognosis, and a number of studies showing insignificant results (Yang *et al.* 2016). Information demonstrating significant differences in the prevalence of these gene alterations between primary and metastatic tumor tissues is limited, while enrichment in metastatic patients is probable (Millis *et al.* 2015).

1.2 BACKGROUND ON IPATASERTIB

Ipatasertib is a potent, highly selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase Akt. Ipatasertib binds to the activated conformation of Akt and is ATP competitive. Ipatasertib binding inhibits the kinase activity of Akt and suppresses the phosphorylation of its direct substrates, including PRAS40, and additional downstream targets, such as S6 ribosomal protein (S6RP), resulting in G_1 arrest and/or apoptosis in human cancer cells (Lin *et al*. 2012). In clinical tumor samples, robust Akt pathway inhibition by ipatasertib can be achieved at clinically relevant doses (Yan *et al.* 2013).

Upregulation of Akt signaling (whether intrinsic or induced following chemotherapy) represents a potentially important survival pathway in response to genotoxic/mitotic stress (Xu *et al*. 2012). Activation of Akt signaling following chemotherapy (including taxanes) may promote cell survival and chemoresistance across several cancer models, including breast cancer (Clark et al. 2002). Conversely, inhibition of the PI3K/Akt pathway in diverse cancers leads to radiosensitization and/or chemosensitization (Brognard *et al.* 2001; Solit *et al.* 2003; Wallin *et al.* 2010).

In nonclinical models with high levels of phosphorylated Akt or PI3K/Akt pathway activity (i.e., *PIK3CA* mutation, *PTEN* alterations), sensitivity to ipatasertib has been observed across different tumor models, including breast cancers (Lin *et al.* 2013). Additionally, ipatasertib plus microtubule inhibitors or DNA-damaging chemotherapeutic agents showed a clear advantage over respective single-agent treatment in preclinical models (refer to the Ipatasertib Investigator's Brochure for further information).

Based on the scientific rationale that PI3K/Akt blockade attenuates survival signals associated with mitotic stress from treatment with microtubule inhibitors and the high prevalence of PI3K/Akt pathway activation signatures in TNBC and in HR+/HER2− tumors (Cancer Genome Atlas Network, 2012), clinical trials evaluating the preliminary safety and efficacy of the combination of ipatasertib and paclitaxel in patients with breast cancer have been conducted. These trials include a Phase Ib study with an expansion

cohort of patients with HER2− breast cancer (Study PAM4983g, Arm C) and a randomized Phase II study (GO29227, LOTUS) comparing ipatasertib + paclitaxel versus placebo + paclitaxel as first-line treatment for patients with inoperable locally advanced or metastatic TNBC.

In the Phase Ib study PAM4983g, 3 of the 15 patients (20%) with breast cancer remained progression free for > 6 months (HR+/HER2−: n = 2; TNBC: n = 1), and 4 partial responses included patients who had prior exposure to paclitaxel or investigational PI3K inhibitors (HR+/HER2−: n = 2; TNBC: n = 2).

In the randomized Phase II study GO29227, one of the objectives was to investigate the added benefit of ipatasertib to paclitaxel in the subgroup of patients with *PIK3CA/AKT1/PTEN*-altered tumors. Results from this study showed improvement in median PFS in the intent-to-treat (ITT) population (hazard ratio = 0.60; 6.2 months in the ipatasertib arm compared with 4.9 months in the control arm); and more pronouncedly in the pre-specified patient population with *PIK3CA/AKT1/PTEN*-altered tumors (hazard ratio = 0.44; 9 months vs. 4.9 months).

Refer to the Ipatasertib Investigator's Brochure for details on nonclinical and clinical studies, including single-agent activities in the Phase I study (PAM4743g).

1.3 BACKGROUND ON CARBOPLATIN

DNA-damaging agents such as platinum drugs (cisplatin and carboplatin) are active in TNBC. The randomized TNT trial, single-agent carboplatin was compared to single-agent docetaxel in patients with metastatic TNBC. Patients with TNBC and germline *BRCA1/2* mutations were found to have a higher response rate and longer progress-free survival rates favoring carboplatin over docetaxel (Tutt *et al.* 2015). Weekly paclitaxel (100mg/m2) was combined with weekly carboplatin AUC 2, days 1, 8, and 15 on a 4 week schedule in a cohort of advanced breast cancer patient. The regimen was effective with a response rate of 62% and well tolerated with a grade ¾ neutropenia rate of 35%. Other grade 3/4 toxicities included neuropathy (11%), infection (6%), weakness (6%), anemia (5%), and paresthesia (3%) (Loesch *et al.* 2002). This study showed that weekly carboplatin/ paclitaxel produces response rates comparable with those seen with the q3w schedule, but with a more favorable toxicity profile (Loesch *et al.* 2002). A high proportion of TNBC tumor exhibit BRCAness-like status, which indicate these tumors are highly sensitive to platinum salts.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT FOR ARM A AND B

Metastatic breast cancer remains an incurable disease. For patients with locally advanced and metastatic TNBC, clinical outcome is particularly poor, generally with rapid progression and a median OS of approximately 16 months (Rodler *et al.* 2010;

Miles *et al*. 2013). For patients with HR+/HER2− breast cancer who are not appropriate candidates for endocrine therapy, OS with first-line chemotherapy with weekly single-agent paclitaxel is approximately 28 months (Miles *et al.* 2013; Miles *et al.* 2017).

Results of the Phase II randomized Study GO29227 demonstrated that adding ipatasertib to paclitaxel as first-line therapy for inoperable locally advanced or metastatic TNBC improves PFS in the ITT and in PTEN-low populations; the PFS improvement was more pronounced in patients with *PIK3CA/AKT1/PTEN*-altered tumors identified with the FoundationOne next-generation sequencing (NGS) assay (representing approximately 40% of the randomized patients in this setting). The use of *PIK3CA/AKT1/PTEN*-alteration status as a predictive biomarker for response to the combination of ipatasertib and paclitaxel in metastatic TNBC is further supported by the pronounced PFS improvement over the complementary population of patients with *PIK3CA/AKT1/PTEN* non-altered tumors.

The clinical safety profile of ipatasertib as a single agent in the Phase Ia study (PAM4743g) and in combination with paclitaxel in the Phase Ib (PAM4983g) and Phase II (GO29227) studies supports continued development in metastatic breast cancer. As a single agent, ipatasertib has a predictable pharmacokinetic (PK) profile with a half-life of approximately 48 hours and significantly downregulates the PI3K/Akt pathway at doses ≥200 mg. In Study GO29227, the adverse effects of ipatasertib plus paclitaxel in metastatic TNBC were consistent with previous experiences of ipatasertib and of paclitaxel, most notably ipatasertib-related gastrointestinal toxicities that are manageable and reversible. Common adverse events with a ≥10% higher incidence in the ipatasertib arm than in the placebo arm were diarrhea, nausea, asthenia, and peripheral sensory neuropathy. Common Grade ≥3 adverse events included diarrhea, neutropenia, neutrophil count decreased, and fatigue. When grouping the adverse event preferred terms with similar medical concepts, asthenia/fatigue and peripheral neuropathy were not significantly different between the two arms (refer to the Ipatasertib Investigator's Brochure for detailed safety information).

In Study GO29227, diarrhea was more common in the ipatasertib arm compared with the placebo arm (93% vs. 19%); however, the majority of cases were low grade. The onset of diarrhea was most common within the first cycle; late onset diarrhea was rare, and no cases of colitis were reported. Diarrhea generally responded to loperamide treatment and to ipatasertib dose holds and dose reductions when resuming treatment; limited (only 3%) discontinuation of ipatasertib treatment due to diarrhea was reported. Despite the high frequency of diarrhea in the ipatasertib arm, the median relative dose intensity of both ipatasertib and paclitaxel approached 100% and was comparable in the ipatasertib and placebo arms.

In current studies, to improve diarrhea management and patient experiences, anti-diarrhea prophylaxis (loperamide) has been mandated for the first cycle for all patients (where allowed by local guidance) and implemented subsequently as clinically

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indicated. Patients are being monitored for early signs of diarrhea symptoms, and investigators will be provided with comprehensive management guidelines for study treatment–related symptoms or potential risks.

Based on the efficacy of carboplatin in TNBC, and prior Phase II data (GO29227) in patients with TNBC support the addition of ipatasertib to carboplatin treatment in patients with metastatic TNBC. Our preclinical data in patient derived xenograft model of metastatic TNBC, carboplatin and ipatasertib were synergistic in tumor suppression (Yuan *et al.* unpublished data). Based on these evidence, we hypothesize that carboplatin or carboplatin/paclitaxel plus the Akt inhibitor ipatasertib will have a synergistic effect in TNBC. Hence this clinical trial is designed to test the safety of the doublet and triplet combination and obtain initial evidence of efficacy. The combination of ipatasertib and paclitaxel has been generally well tolerated and comprehensive guidelines for management of anticipated treatment-related symptoms will be incorporated into this protocol building upon previous clinical trial experience. Preliminary data suggests a better response to ipatasertib in patients with PIK3CA/AKT1/PTEN altered breast tumors. DNA targeted exome-sequencing will be used for detecting genomic alterations. TNBC sub-typing will be performed through mRNA profiling. These genomic alterations will be associated with clinical responses.

This trial will enroll patients with metastatic triple negative breast cancer. Given the relatively poor prognosis and limited treatment options for these patients, this population is considered appropriate for trials of novel therapeutic candidates. The benefit-risk ratio for ipatasertib in combination with carboplatin or carboplatin/ paclitaxel is expected to be acceptable in this setting.

1.5 Background on Arm C

Capecitabine and Immune Checkpoint Inhibitor: The Impassion130 study demonstrated the addition of immune checkpoint inhibitor atezolizumab (anti-PD-L1) to nab-paclitaxel improved PFS in PD-L1 positive mTNBC in the first line setting.(3) It remains unknown whether non-taxane chemo + anti-PD-1/L1 will be beneficial in mTNBC. In the curative setting, evidence has emerged from the CREATE-X study that supports the use of adjuvant capecitabine for patients who have residual disease after standard neoadjuvant chemotherapy (containing anthracycline, taxane, or both). In this trial, eight q3 weekly cycles of adjuvant capecitabine therapy was shown to be safe and effective in prolonging disease-free survival and overall survival among patients with HER2-negative breast cancer who had residual invasive disease.(4) Given these data, as well as promising data supporting the use of immune checkpoint inhibition (ICI) in TNBC, there is a strong interest in testing the combination of an ICI in combination with capecitabine. In fact, a phase Ib study of metastatic breast cancer, pembrolizumab plus capecitabine (2000mg bid, 7 days on and 7 days off) showed encouraging safety and efficacy. Overall response for the capecitabine+ pembrolizumab arm was 43% (5 PR, 1 CR, 2 SD) with median progression free survival of 155 days.(5)

Combination of AKT inhibitor with ICI: PTEN is a well-known negative regulator of AKT. PTEN loss is associated with decreased T cell infiltration and reduced efficacy of ICI. PI3K-beta inhibitor improves the efficacy of both anti-PD-1 and anti-CTLA-4, supporting the rationale of

exploring combinations of ICI and PI3K/AKT pathway inhibitors(17). In a phase IB study, the combination of ipatasertib, atezolizumab and paclitaxel or nab-paclitaxel showed a promising response rate of 73% in a cohort of 26 patients with unresectable, locally advanced/metastatic TNBCs previously untreated in the metastatic setting. Interestingly, responses were high irrespective of PD-L1 status or PI3K/AKT/PTEN alteration status(2).

In the third arm of this study, arm C, we aim to test the combination of ipatasertib, capecitabine and atezolizumab in patients with PD-L1 mTNBC. The primary end point will be safety and tolerability of the regimen. Identifying the safe dose of these three drugs in combination will pave the way to evaluate this triplet combination in early stage disease. A secondary endpoint will be the response rate and evaluation of the role of PD-L1 status.

2. OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE(S)

Phase I:

To determine the recommended Phase II dose (RP2D) of ipatasertib plus carboplatin/paclitaxel (arm A), ipatasertib plus carboplatin (arm B), and ipatasertib, atezolizumab, and capecitabine (arm C) in patients with metastatic TNBC.

Phase IB:

- To obtain initial evidence of activity by examining progression free survival for each dose regimen

2.2 SECONDARY OBJECTIVE(S)

- To confirm the RPIID safety in expanded cohort by evaluating toxicities and confirm tolerability of the combinations

- To obtain evidence of activity by examining response rate based on RECIST 1.1.

- To evaluate clinical benefit rate (CBR), event-free survival, time-to-treatment failure and overall survival
- Further describe the cumulative toxicities (CTCAE 5.0) of the combinations.
- To evaluate patient's quality of life (QOL)

2.3 EXPLORATORY OBJECTIVE(S)

- To evaluate the progression-free survival and overall survival, based on the genomic alterations including *PIK3CA/AKT/PTEN* alterations and BRCA status.

- To study the association of TNBC mRNA expression profiling including Vanderbilt molecular subtype and treatment response

- To study the association of stool microbiome, calprotectin with diarrhea

- To study peripheral blood circulating tumor DNA

- To study therapy resistance by analyzing tumor genomics and transcriptome analysis

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- To study the profiles of peripheral blood mononuclear cells and its association with response to therapy

- To study genomic immune biomarkers and its association with response

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase I trial of ipatasertib plus either carboplatin or carboplatin/ paclitaxel in patients with metastatic TNBC. The combination of paclitaxel and ipatasertib have been well-tolerated and the recommended phase II dose is ipatasertib 400mg po daily 3 weeks on/1 week off, paclitaxel 80mg/m2 days 1, 8,15 of every 4 week cycle based on the previous data of LOTUS trial. In the current trial, two dosing regimen will be tested in this study. In triplet schedule A, carboplatin AUC 2, paclitaxel 80mg/m2 will be added on day 1, 8 and 15 of every 4 weeks cycle while patients receive ipatasertib of 400mg daily. In doublet schedule B, carboplatin AUC 2 on days 1, 8, 15 every 28 days will be added to ipatasertib 400mg daily continuous dosing.

We will use the Phase I Queue (IQ) 3+3 design that insures patient risk does not exceed the maximum risk permitted in the traditional 3+3 design, while enabling fewer study holds and permits the PI to proceed with a more rapid completion of the Phase I study. A variety of 3-at-risk designs have been conducted, including NCI/CTEP studies based on the 3+3 risk constraints (NCT02568553, NCT01567709). This method has been shown (presented at JSM 2016, with the latest design presented at JSM 2018, Frankel, P, Activity #359, manuscript submitted) to reduce study duration by an average of approximately 23% for a typical Phase I study, with a median increase in the number of patients of 1-4, while reducing the number of patients turned away due to lack of slots. The operating characteristics demonstrate negligible difference in the dose chosen for the MTD, and in the number of DLTs reported in patients treated above the MTD (see statistical considerations). The details of the design are described below (**D**: Comparison of the 3+3 and the Phase I Queue 3+3 (IQ 3+3) Design Decisions).

For response and PFS estimates, and to confirm the recommended Phase II dose obtained from the dose escalation, we will enroll an additional cohort of patients until the number treated and evaluable for DLT considerations at the recommended phase II dose is 14 patients for the doublet (**Table B**) and for the triplet schedules (**Table A**).

All eligible patients who start treatment at the recommended dose will be considered in the calculation of the response rate.

Sample size for the doublet and triplet schedules A and B: Expected sample size (if level 1 is well-tolerated) is 14 patients for both the doublet and triplet, for an expected total sample-size of 28 patients. Additional cohorts of 6-8 patients are required if level 1 is not well-tolerated for each schedule.

Sample-size for the triplet Arm C: The starting dose level for schedule C is not the highest possible dose to be tested, which differs from Arm A and B. Once the MTD and recommended phase 2 dose (RP2D) is selected for Arm C, at least 12 total patients will be treated at the RP2D. The expected number of patients (based on 800 simulations with DLT rates of 9.0%, 10.8%, 13.6% and 18.0% or with DLT rates of 6.7%, 7.6%, 9.0% and 10.8% for levels 1-4) is between 17 and 18 patients for dose-finding, and the interquartile range is 15-20 patients. If after 12 patients have been accrued to the RP2D in total, the number of total patients remains less than 21, additional patients can be accrued to the RP2D (e.g. if the RP2D is dose level 1, with 6 patients treated, and 2 DLTs on dose level 2 for a total 8 patients, 13 additional patients can be added to dose level 1 as opposed to only 6).

Table A. Arm A levels

Arm A	Ipatasertib (oral)	Carboplatin/Paclitaxel
1	400mg po daily	Carboplatin AUC 2 Paclitaxel 80 mg/m2, days 1, 8, 15 every 4 weeks
-1A‡	400mg po daily	Carboplatin AUC 1.5, Paclitaxel 65 mg/m2, days 1, 8, 15 every 4 weeks
-1B†	300 mg po daily	Carboplatin AUC 2, Paclitaxel 80 mg/m2, days 1, 8, 15 every 4 weeks
-1C*	300 mg po daily	Carboplatin AUC 1.5, days 1, 8, 15 Paclitaxel 65 mg/m2, days 1, 8, 15 every 4 weeks
-1D**	300 mg po daily	Carboplatin AUC 1.5, days 1, 15 Paclitaxel 65 mg/m2, days 1, 15 every 4 weeks

‡ Dose reduction to level -1A if DLTs require de-escalation and are attributed to carboplatin/paclitaxel (such as myelosuppression, neuropathy, intolerance to carboplatin/paclitaxel infusion reaction)
†Dose reduction to level -1B if DLTs require de-escalation and are attributed ipatasertib (such as diarrhea, hyperglycemia)
*Dose reduction to level -1C if DLTs require de-escalation and other high-grade toxicities relate to both carboplatin/paclitaxel and ipatasertib, or if levels -1A or -1B are not well-tolerated (e.g. >1 DLT in 6 patients).
**Dose reduction to level -1D if DLTs require de-escalation and are on level -1C.

Table B. Arm B levels

Arm B	Ipatasertib (oral)	Carboplatin
1	400mg po daily	AUC 2 on days 1, 8, 15 every 28 days
-1A‡	400 mg po daily	AUC 1.5 on days 1, 8, 15 every 28 days
-1B†	300 mg po daily	AUC 2 on days 1, 8, 15 every 28 days
-1C*	300mg po daily	AUC 1.5 on days 1, 8, 15 every 28 days
-1D**	300mg po daily	AUC 1.5 on days 1, 15 every 28 days

‡ Dose reduction to level -1A if DLTs require de-escalation and are attributed to carboplatin (such as myelosuppression, neuropathy, intolerance to carboplatin infusion reaction)
†Dose reduction to level -1B if DLTs require de-escalation and are attributed ipatasertib (such as diarrhea, hyperglycemia)
*Dose reduction to level -1C if DLTs require de-escalation and other high-grade toxicities relate to both carboplatin and ipatasertib, or if levels -1A or -1B are not well-tolerated (e.g. >1 DLT in 6 patients).
**Dose reduction to level -1D if DLTs require de-escalation and are on level -1C.

Table C. Arm C levels

Arm C	Drug Dosage		
	Ipatasertib	Capecitabine	Atezolizumab
Dose Level -1	200 mg daily days 1-21	750 mg/m2 Bid, 1 week on 1 week off x 2	840 mg IV d1 and 15
Dose Level 1 (starting dose)	300 mg daily days 1-21	750 mg/m2 Bid, 1 week on 1 week off x 2	840 mg IV d 1 and 15
Dose Level 2	400 mg daily days 1-21	750 mg/m2 Bid, 1 week on 1 week off x 2	840 mg IV d1 and 15
Dose Level 3	400 mg daily days 1-21	1000 mg/m2 Bid, 1 week on 1 week off x 2	840 mg IV d1 and 15

28 days each cycle

Table D: Comparison of the 3+3 and the Phase I Queue 3+3 (IQ 3+3)

Design Decisions # on Current Level			IQ 3+3[b,c]: Dose Level for Next Pt.	3+3[b]: Dose Level for Next Pt.
Total[a]	EVAL	DLT		
0-2	0	0	Same dose level	Same dose level
3	0	0	Hold accrual	Hold accrual
1-2	1	0	Same dose level	Same dose level
3	1	0	***Same dose level***	***Hold accrual***
4	1	0	***Hold accrual***	-- not allowed
2	2	0	Same dose level	Same dose level
3	2	0	***Same dose level***	***Hold Accrual***
4-5	2	0	***Same dose level***	-- not allowed
6	2	0	***Hold accrual***	-- not allowed
3	3	0	Escalate[d]	Escalate[d]
4-6	3-5	0	Escalate[d]	Same dose level (closed above)
6	6	0	Escalate (or MTD)[d]	MTD
1-2	1	1	Same dose level	Same dose level
3	1	1	Hold Accrual	Hold Accrual
2	2	1	Same dose level	Same dose level
3	2	1	***Same dose level***	***Hold Accrual***
4	2	1	***Hold accrual***	-- not allowed
3-5	3-5	1	Same dose level	Same dose level
6	3	1	Hold accrual	Hold accrual
6	4	1	***Same dose level***	***Hold accrual***
6	5	1	***Same dose level***	***Hold accrual***
7	4	1	***Hold accrual***	-- not allowed
7	5	1	***Same dose level***	-- not allowed
6-8	6-8	1	Escalate[d]	Escalate[d] (pt 7,8 not allowed)
2-7	2-6	2	De-escalate[e]	De-escalate[e] (pt 7 not allowed)
7	7	2	***MTD***	-- not allowed
8	7	2	***Hold accrual***	-- not allowed
8	8	2	***MTD***	-- not allowed
any	Any	3	De-escalate[e]	De-escalate[e]

[a]Total number of patients consented, excluding proven screen failures or patients inevaluable for DLT. [b]PI can hold accrual at any time for pending patients to complete evaluation. [c]If a patient pending evaluation on a lower dose experiences a DLT, the PI, in consultation with the sponsor, may choose to reduce the dose of any patients currently on a higher dose pending review of the AE data. [d] If the next higher dose level is not available (there is no higher dose or the higher dose was already tested and too toxic), treat at current dose and declare the MTD with 0 or 1 DLT out of 6 (or 0 out of 5). For IQ3+3 no more than 4 patients at risk.2 DLTs out of 7 or 8 patients can also declare the MTD. [e]Current level exceeds the MTD. The MTD is the highest level at which <33% of patients had DLTs, with at least 6 evaluable patients.

Ipatasertib will be administered at the starting dose of 400 mg orally once daily, on Days 1–28 of each 28-day cycle or ipatasertib will be administered at the starting dose of 300 mg orally once daily on a continuous dosing schedule until the patient experiences disease progression, intolerable toxicity, elective withdrawal from the study treatment, or elective withdrawal from the study. Ipatasertib may be dosed 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.

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Table E: Type of Study Drug

Type of Study Drug	Compound	Min Dose	Max Dose	Frequency	Admin Route
Investigational	Ipatasertib	300mg	400mg	Daily	Oral
Standard of care	Arm A: Carboplatin Paclitaxel Arm B: Carboplatin Arm C: Capecitabine Atezolizumab	AUC1.5 65mg/m2 AUC1.5 750 mg/m2 Bid 840mg	AUC 2 80mg/m2 AUC 2 1000 mg/m2 Bid 840mg	Days 1, 8, 15* every 4 weeks Days 1, 8, 15* every 4 weeks Day 1, 8, 15* every 4 weeks	iv iv iv Oral 1wk on 1 wk off iv
Supportive†	Imodium				Oral

* If Dose not tolerated, day 8 dose can be skipped

† Standard of care, not provided by study supply

Carboplatin or Carboplatin/paclitaxel dose will be given as listed on above tables.

Patients will undergo tumor assessments at scheduled intervals during the study (see **Section 4.5** and **Appendix 1** study calendar for details). Patients who have dose modifications per protocol plan and do not experience a DLT will be considered non-DLTs for the purposes of the Phase I dose evaluation.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs; or the required number of events for the final analysis of OS has occurred; or all patients meet one of the following criteria: patient has experienced an OS event, patient has become lost to follow

up, patient has withdrawn consent, or patient has completed at least 24 months of follow-up after start of treatment. The end of the study is expected to occur 18 months after the last patient is enrolled. In addition, the Investigator may decide to terminate the study at any time.

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 36 months.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Ipatasertib

In previous studies, the ipatasertib starting dose of 400 mg QD on Days 1–21 of each 28-day cycle was selected on the basis of safety and pharmacokinetics data from Arm C of Study PAM4983g (Phase Ib trial of ipatasertib combined with paclitaxel; refer to the Ipatasertib Investigator's Brochure for details). The pharmacokinetics of paclitaxel and ipatasertib following co-administration showed no evidence of drug–drug interaction and 400 mg ipatasertib was better tolerated than 600 mg ipatasertib in this combination.

In the randomized, placebo-controlled Phase II study (GO29227) in patients with locally advanced or metastatic TNBC, the combination of ipatasertib 400 mg administered QD on Days 1–21 of each 28-day cycle and paclitaxel 80 mg/m^2 administered weekly on Days 1, 8, and 15 of each 28-day cycle was generally well tolerated and showed an improvement in PFS. The sparse sampling exposure results in this study were also consistent with the known PK profiles of ipatasertib (and its metabolite G-037720).

In addition, the totality of pharmacodynamics data from Phase I (PAM4743g, PK/pharmacodynamic analysis) and safety and efficacy data (including exploratory exposure-response analyses, data on file) from randomized Phase II studies of ipatasertib (Study GO29227 and Study GO27983, which evaluated two dose levels of 200 mg and 400 mg of ipatasertib in patients with metastatic castration-resistant prostate cancer) support the selected starting dose of 400 mg ipatasertib for sufficient pathway inhibition and efficacy with a generally acceptable safety profile (refer to the Ipatasertib Investigator's Brochure for details). In the ipatasertib + paclitaxel arm of the GO29227 study, despite dose reduction of ipatasertib that occurred in 21.3% of patients due to adverse events, discontinuation of ipatasertib due to any adverse event was 6.1%, and the median cumulative dose intensity of both ipatasertib and paclitaxel were maintained at 99.0% (ipatasertib) and 100% (paclitaxel).

The ipatasertib starting dose of 400 mg daily was selected based on safety data from the Phase Ib portion of the study GO27983. Ipatasertib at the 400-mg dose level has generally been well tolerated in combination with abiraterone and prednisone. The most common AEs reported were Grade 1 and Grade 2 gastrointestinal symptoms, including nausea, vomiting, and diarrhea. These may be managed effectively with standard supportive care. Overall, the spectrum and frequency of AEs attributable to ipatasertib in combination with abiraterone is similar to that of single-agent ipatasertib in the PAM4743g trial.

The patients treated at the 400 mg dose of ipatasertib achieved a similar plasma exposure at steady-state relative to patients treated at 400–600 mg on a 21-of-28 day schedule (the single-agent MTD). At 400 mg daily, the cumulative ipatasertib dose administered over 28 days is similar to that at 600 mg dosed on a 21-of-28 day schedule. Significant pathway inhibition was demonstrated at the 400 mg dose level (for further details, see the Ipatasertib Investigator's Brochure).

In the current study, ipatasertib continuous dosing for arms A and B was planned in order to better understand the tolerability of the daily dosing in combination with chemotherapy. Hypothetically continuous AKT inhibiting may provide sustained target suppression and possible improved disease control. Therefore the dosing schedules of this clinical trial were selected based on continuous dosing of ipatasertib. For Arm C, to be consistent with LOTUS and ongoing phase III trials, ipatasertib 3 weeks on, 1 week off schedule was chosen. Due to concerns of increased risk of diarrhea, ipatasertib starting dose of 300mg was chosen.

3.3.2 Rationale for Carboplatin/Paclitaxel or Carboplatin

Carboplatin combination therapy has been shown to be effective in treatment of metastatic breast cancers (Perez *et al.* 2004). Weekly paclitaxel (100mg/m2) was combined with weekly carboplatin AUC 2, days 1, 8, and 15 on a 4 week schedule in a cohort of advanced breast cancer patient. The regimen was effective with a response rate of 62% and well tolerated with a grade 3/4 neutropenia rate of 35%. Other grade 3/4 toxicities included neuropathy (11%), infection (6%), weakness (6%), anemia (5%), and paresthesia (3%) (Loesch *et al.* 2002). In the LOTUS trial, grade 3/4 neutropenia rate was 10%. There is a strong rationale to test continuous dosing of ipatasertib for consistent AKT inhibition. Therefore in the current study, we proposed two dosing schedules to study the combination of carboplatin alone with ipatasertib or carboplatin/paclitaxel in combination with continuous dosing of ipatasertib. Starting doses for each combination and the dosing schedules are described in detail in **section 3.1**.

Single agent activity of carboplatin in breast cancer has been extensively studied. In several phase II studies of patients with metastatic breast cancer, single-agent carboplatin produced objective response rates of 20%–35% in previously untreated patients (Kolaric *et al.* 1991, Martin *et al.* 1992, O'brien *et al.* 1993) at dosing of 400 mg/m^2 every 3 or 4 weeks, or based on glomerular filtration rate to achieve an area under the concentration-versus-time curve (AUC) of 7 mg/ml minute every 4 weeks. In contrast, objective responses were 8-16% with these carboplatin schedules in patients treated previously with chemotherapy for metastatic disease (O'brien *et al.* 1993, Carmo-Pereira *et al.* 1990).

3.3.3 Rationale for Capecitabine and Atezolizumab

In CREATE-X trial, adjuvant capecitabine treatment was shown to be safe and effective in prolonging disease-free survival and overall survival among patients with HER2-negative breast cancer who had residual invasive disease. A phase Ib study of pembrolizumab plus capecitabine (2000mg bid, 7 days on and 7 days off) showed encouraging safety and efficacy.

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Overall response for the capecitabine+ pembrolizumab arm was 43% (5 PR, 1 CR, 2 SD) with median progression free survival of 155 days.[3] Since both capecitabine and ipatasertib are associated with diarrhea, a lower dose of capecitabine starting dose at 750mg/m2 will be used. Capecitbine 7 days on and 7 day off schedule is based on the following publication: Traina TA, Dugan U, Higgins B, Kolinsky K, Theodoulou M, Hudis CA, Norton L. Optimizing chemotherapy dose and schedule by Norton-Simon mathematical modeling Breast disease. 2010 Jan 1;31(1):7-18. Detailed dosing schedules are described in detail in **section 3.1**. Atezolizumab dose was selected based on Impassion 130 trial and FDA package insert.

3.3.4 Rationale for Patient Population

Despite multiple treatment options, advanced breast cancer remains an incurable disease. Although chemotherapy is a mainstay treatment for TNBC, resistance inevitably develops and benefit is often short-lived. Ipatasertib with paclitaxel has shown encouraging clinical benefit for TNBC from the randomized Phase II study (GO29227 or LOTUS). In Study GO29227, patients with TNBC in the ipatasertib + paclitaxel arm showed a more pronounced improvement in PFS in the pre-specified patient population with PIK3CA/AKT1/PTEN-altered tumors (hazard ratio = 0.44, 9.0 months vs. 4.9 months) compared with PIK3CA/AKT1/PTEN non-altered tumors (hazard ratio = 0.76, 5.3 months vs. 3.7 months) or unselected ITT patients (hazard ratio = 0.60, 6.2 months vs. 4.9 months).

For patients with metastatic HR+/HER2− breast cancer, approved therapy during the endocrine-sensitive phase includes CDK4/6 inhibitors and PI3K/Akt pathway inhibitors such as everolimus. Preliminary data from the Phase Ib study PAM4983g suggest that HR+/HER2− patients may still respond to the combination of ipatasertib + paclitaxel after prior exposure to PI3K/Akt pathway inhibitors (e.g., PI3K inhibitors) (Isakoff *et al.* 2014). The efficacy of ipatasertib for patients previously treated with CDK4/6 inhibitors is unknown, but these patients are not excluded from participation in this study.

3.3.5 Rationale for Biomarker Assessments

Genomics: Genomic analysis is increasingly informing our understanding of disease pathobiology. Next-generation sequencing (NGS) such as whole exome sequencing (WES) provides a comprehensive characterization of the exome, and along with clinical data collected in this study, may provide the opportunity to develop new therapeutic approaches. Triple negative breast cancer is a heterogeneous disease with many distinct subtypes as defined by molecular signatures and a diverse array of mutational profiles.

In addition to *PIK3CA/AKT1/PTEN*–alteration status, samples will be assessed for additional biomarkers in an effort to identify factors that may correlate with the safety and efficacy of treatment with ipatasertib combined with carboplatin or carboplatin/paclitaxel.

In addition, all submitted tumor or blood samples at screening and end-of-study may be evaluated using additional genomic testing such as NanoString nCounter Breast Cancer 360 panel and data analysis to provide a more comprehensive understanding of resistance

mechanisms to carboplatin/AKT inhibitor, which may lead to future development of alternative treatment strategies.

Carboplatin has shown significant efficacy in *BRCA1/2* mutated tumors. The BRCA status will also be examined using NGS, WES, and/or other methods. The collected DNA from blood samples and tumor tissue from this study will be analyzed to identify germline (e.g., *BRCA1/2*) and somatic alterations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, or can increase the knowledge and understanding of disease biology.

Gut Microbiome: Recently, it has become evident that the gut microbiota modulates the response to cancer therapy and susceptibility to toxic side effects (Roy *et al.* 2017). The best characterized therapies are oxaliplatin (Tesniere *et al*. 2010) and cyclophosphamide (Daillère *et al.* 2016). The gut microbiota primes myeloid cells for production of reactive oxygen species in the case of oxaliplatin, and facilitates the induction of an anticancer T cell response in the case of cyclophosphamide (Daillère *et al.* 2016). The role of gut microbiota in modulating the response to tyrosine kinase inhibitors remains to be discovered. Evidence of the important role of the microbiota in controlling cancer therapy effectiveness and toxicity is derived mainly from data in experimental animals, and translation of these findings to human clinical medicine remains challenging. Additional clinical data need be obtained in order to understand how ipatasertib affects the gut microbiota, and to develop strategies to attenuate the gastrointestinal side effects of ipatasertib. Therefore, gut microbiota analysis will be included in this study to assess the correlation of treatment side effects such as diarrhea and treatment response. Stool sample will be collected at baseline, C4D1 and end-of-study visit (**Appendix 1 Study Calendar**).

Plasma Calprotectin: Calprotectin, first described in 1980 by Fagerhol, is released by activated neutrophils, and accounts for more than 40% of the cytosolic proteins of neutrophils. Elevated concentrations of calprotectin can be measured in plasma, cerebrospinal fluid, synovial fluid, urine, and feces when ongoing inflammation is present, or in malignant conditions (Fagerhol *et al*. 1980). Increased fecal calprotectin (FCP) concentrations have been found in gastric and colorectal cancers as well as in inflammatory bowel disease (IBD). The high fecal calprotectin concentrations detected in IBD can be explained by increased turnover of leukocytes in the gut wall, and increased migration of neutrophils into the gut lumen. FCP was found to be strongly associated with colorectal inflammation indicating organic disease, and is a simple and non-invasive method for assessing excretion of macrophages into the gut lumen. FCP values can be used to screen asymptomatic patients, evaluate the response to treatment, and predict disease relapse in patients with IBD (Erbayrak *et al.* 2009). It is unclear if FCP is associated with targeted therapy-induced bowel inflammation and/or diarrhea. In this study, FCP analysis will be used for detection of bowel inflammation, by collecting plasma samples at **baseline, C2D1 and end-of-study visit** (**Appendix 1 Study Calendar**).

For gut microbiome collection kit information and instructions, refer to **Appendix 7**. For biospecimen sample transportation, refer to **Appendix 10**.

3.3.6 Rationale for Patient-Reported Outcome Assessments

Patient reported outcomes (PROs) provide an understanding of the impact a treatment has on a patient. The QLQ-C30 is a validated instrument that has been widely used in assessing quality of life in patients with cancer. The core instrument assesses global health status/quality of life, functions (physical, role, emotional, cognitive, and social), and general cancer symptoms. For EORTC QLQ-C30 forms, refer to **Appendix 11**.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 40 patients with metastatic TNBC and PI3K/AKT/mTOR/PTEN alteration will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Age ≥ 18 years at time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Histologically or cytologically confirmed triple negative breast cancer defined by **ER or PR ≤10% by IHC** and **HER2 negative** defined by current ASCO/CAP guideline
- Disease progression during or following treatment with 0- 2 lines of chemotherapy and/or biological targeted therapy in the metastatic setting
- Measurable (Arm C only) or non-measurable (allowed for Arm A or B) but evaluable disease per RECIST v1.1 (Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.)
- **Baseline Tissue requirement**:
    - A formalin-fixed paraffin-embedded (FFPE) tumor specimen in a paraffin block (preferred) or at least **20 x 5µm** slides containing unstained, freshly cut, serial sections must be collected along with an associated pathology report prior to study enrollment.
    - If only 10–19 slides are available, the patient may still be eligible for the study, after Principal Investigator approval has been obtained.
    - If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, tumor tissue must be obtained from a biopsy performed at screening.
    - A biopsy may also be performed at screening if a patient's archival tissue test results do not meet eligibility criteria. Refer to **Section 4.5.6** for additional information on tumor specimens collected at screening.
- ECOG Performance Status of 0-1

- Life expectancy ≥ 3 months
- Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to initiation of study treatment:
  - ANC $\geq 1.5 \times 10^9$/L (1,500/μL) without granulocyte colony-stimulating factor support
  - Platelet count $\geq 100 \times 10^9$/L (100,000/μL) without transfusion
  - Hemoglobin ≥ 9 mg/dL (9 mg/dL) (Patients may be transfused to meet this criterion.)
  - Adequate liver function defined by:
    - AST and ALT $\leq 2.5 \times$ ULN, with the following exception:
    - Patients with documented liver metastases may have AST and ALT $\leq 5 \times$ ULN.
    - ALP $\leq 2 \times$ ULN, with the following exceptions:
    - Patients with known liver involvement may have ALP $\leq 5 \times$ ULN
    - Patients with known bone involvement may have ALP $\leq 7 \times$ UL
    - Serum bilirubin $\leq 1.5 \times$ ULN with the following exception:

    Patients with known Gilbert disease: serum bilirubin level $\leq 3 \times$ ULN
  - Adequate renal function defined by: Serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance ≥ 50mL/min (calculated using the Cockcroft-Gault formula)
  - PTT (or aPTT) and INR $\leq 1.5 \times$ ULN (except for patients receiving anticoagulation therapy)
  - Patients receiving heparin treatment should have a PTT (or aPTT) between 1.5 and $2.5 \times$ ULN (or patient value before starting heparin treatment). Patients receiving coumarin derivatives should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1 to 4 days apart.
  - Fasting total glucose $\leq$ 150 mg/dL
- For women of childbearing potential: agreement 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 6 months after the last dose of study treatment. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom, and agreement to refrain from donating sperm, as defined below:

  With female partners of childbearing potential or pregnant female partners, men must remain abstinent or use a condom during the treatment period and for 6 months after the last dose of study treatment to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inability to comply with study and follow-up procedures
- $\geqslant$ Grade 3 toxicities from previous treatment, not recovered to $\leqslant$ Grade 2 at study entry
- Prior exposure to PI3K/AKT/mTOR pathway inhibitors including but not limited to everolimus, ipatasertib, gedatolisib or alpelisib etc.
- Prior exposure to carboplatin for treatment of metastatic TNBC not allowed; prior treatment of carboplatin as neoadjuvant or adjuvant therapy allowed if last dose of therapy completed $\geqslant$ 12 months prior to initiation of the current study
- Prior exposure to paclitaxel or nab-paclitaxel for treatment of metastatic TNBC not allowed for Carboplatin/paclitaxel arm; prior treatment of paclitaxel or nab-paclitaxel as neoadjuvant or adjuvant therapy allowed if last dose of therapy completed $\geqslant$ 12 months prior to initiation of the current study
- Prior exposure to capecitabine for treatment of metastatic TNBC not allowed for Arm C; prior treatment of capecitabine as adjuvant therapy allowed if the last dose of therapy completed $\geqslant$ 12 months prior to initiation of the current study for Arm C
- Prior treatment with immune check point inhibitors for Arm C
- Prior treatment with CD137 agonists or immune checkpoint blockade therapies, including anti–CTLA-4, anti–PD-1, and anti–PD-L1 therapeutic antibodies
- Prior Treatment with systemic immunostimulatory agents (including, but not limited to, interferon and interleukin 2 [IL-2]) within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment for Arm C
- Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti–TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions for Arm C:
  - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of

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corticosteroids for a contrast allergy) are eligible for the study after Medical Monitor confirmation has been obtained

- Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study

- Active autoimmune disorders requiring steroid dose higher than prednisone 10mg daily for Arm C
- Active disease or receiving treatment for hepatitis B or C or HIV infection for Arm C
- Receipt of a live, attenuated vaccine within 4 weeks prior to enrollment (start of treatment), during treatment, or within 5 months following the last dose of atezolizumab for Arm C
- Known allergy or hypersensitivity to any component of carboplatin and/or paclitaxel or nab-paclitaxel, or capecitabine (5-FU) formulation [for patients planned for the respective arms]
- Known dihydropyrimidine dehydrogenase (DPD) deficiency in patients selected to receive capecitabine for Arm C
- Known severe allergic reactions to cisplatin or other platinum-containing compounds or mannitol [for patients planned for platinum-containing arms]
- History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins
- Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab formulation
- History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills
- Active infection requiring systemic anti-microbial treatment (including antibiotics, anti-fungals, and anti-viral agents)
- Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia
- Known untreated or unstable brain metastasis or leptomeningeal metastasis from metastatic breast cancer
- Uncontrolled tumor-related pain
- Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently)

  Patients with indwelling catheters (e.g., PleurX®) are allowed.
- Uncontrolled or symptomatic hypercalcemia (ionized calcium $>$ 1.5 mmol/L, calcium $>$ 12 mg/dL, or corrected calcium $>$ ULN)

- Active or history of autoimmune disease or immune deficiency, including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis with the following exceptions:

  Patients with a history of autoimmune-related hypothyroidism who are on thyroid-replacement hormone are eligible for the study.

  Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.

  Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:

  – Rash must cover $<$ 10% of body surface area
  – Disease is well controlled at baseline and requires only low-potency topical corticosteroids
  – No occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high-potency or oral corticosteroids within the previous 12 months

- History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan

  History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

- Active tuberculosis
- Known HIV infection
- Known clinically significant history of liver disease consistent with Child-Pugh Class B or C, including active viral or other hepatitis (e.g., positive for hepatitis B surface antigen [HBsAg] or hepatitis C virus [HCV] antibody at screening), current drug or alcohol abuse, or cirrhosis

  Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive hepatitis B core antibody [HBcAb] test, accompanied by a negative HBV DNA test) are eligible.

  Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

- Prior allogeneic stem cell or solid organ transplantation
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 of Cycle 1 or anticipation of need for a major surgical procedure during the course of the study

  Placement of a vascular access device is not considered major surgery.

- Pregnant or breastfeeding, or intending to become pregnant during the study or within 28 days after the last dose of ipatasertib, 5 months after the last dose of atezolizumab and within 6 months after the last dose of paclitaxel, whichever occurs later

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Women of childbearing potential (who are not postmenopausal with ≥ 12 months of non-therapy induced amenorrhea nor surgically sterile) must have a negative serum pregnancy test result within 96 hours prior to Day 1 of Cycle 1 treatment.

- New York Heart Association Class II, III, or IV heart failure; left ventricular ejection fraction < 50%; or active ventricular arrhythmia requiring medication
- Current unstable angina or history of myocardial infarction within 6 months prior to Day 1 of Cycle 1 and cerebrovascular accident within 3 months prior to Day 1 of cycle 1
- Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) > 480 milliseconds
- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion (including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction)
- Need for chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease
- Treatment with approved or investigational cancer therapy within 14 days prior to Day 1 of Cycle 1
- Patients with a prior diagnosis of malignancy except non-melanomatous skin cancer treated ⩾ 5 years ago are eligible, provided that they have not received prior taxanes or carboplatin as part of their prior treatment regimen, and that they meet all eligibility criteria.
- Any other disease, physical examination finding, or clinical laboratory finding that, in the investigator's opinion, gives reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- Pregnant or breastfeeding, or intending to become pregnant during the study or within 6 months after the last dose of study treatment

  Women of childbearing potential must have a negative serum pregnancy test result within 14 days prior to initiation of study treatment.

Ipatasertib-Specific Exclusion Criteria

Patients who meet any of the following ipatasertib-specific criteria will be excluded from study entry:

- History of Type I or Type II diabetes mellitus requiring insulin

  Patients who are on a stable dose of oral diabetes medication ≥ 2 weeks prior to initiation of study treatment are eligible for enrollment.
- Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia
- History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)

- Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia)
- Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 2 weeks or 5 drug-elimination half-lives, whichever is longer, prior to initiation of study drug
- Inability to swallow pills
- Malabsorption syndrome

4.2 METHOD OF TREATMENT ASSIGNMENT

This is a Phase I open-label study on two regimens, with expansion cohorts. Neither patients nor investigators are blinded as to the doses or treatment. The cohort with the earlier open slot will be filled first. If slots opened at the same time (or during the expansion cohorts), a physician discretion will determine treatment arm.

4.3 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is ipatasertib and carboplatin +/- paclitaxel. Paclitaxel and carboplatin are approved treatment for breast cancer and are considered standard of care in the United States.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Ipatasertib

The Ipatasertib Drug Product will be supplied by Genentech, Inc. as 100- and 200-mg tablets..

4.3.1.2 Carboplatin

Carboplatin will be supplied through standard commercial supply. For information on the formulation and handling of carboplatin, see FDA package insert.

4.3.1.3 Paclitaxel

Paclitaxel will be supplied through standard commercial supply. For information on the formulation, packaging, and handling of paclitaxel, see FDA package insert.

4.3.1.4 Capecitabine

Capecitabine will be supplied through standard commercial supply. For information on the formulation, packaging, and handling of capcitabine, see FDA package insert.

4.3.1.5 Atezolizumab

Atezolizumab will be supplied by Genentech. For information on the formulation, packaging, and handling of atezolizumab, see FDA package insert.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. Patients who experience an infusion-related reaction (IRR) with the first infusion may receive premedication

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with antihistamines or antipyretics or analgesics (e.g., acetaminophen) for subsequent infusions. The initial dose of atezolizumab will be delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion-associated adverse events or 60 (± 15) minutes if the patient experienced an infusion-associated adverse event with the previous infusion. Vital signs are to be measured before, as well as during, and after infusions, if clinically indicated.

Atezolizumab must be prepared under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The prepared solution for infusion should be used immediately to limit microbial growth in case of potential accidental contamination. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user. For flat or fixed dosing, (e.g., 800 mg, 840 mg, or 1200 mg) in 250 mL IV infusion bags, the dose solution may be stored at 2°C-8°C (36°F-46°F) for 24 hours or at ambient temperature ≤ 25C° (77°F) for 8 hours. This time includes storage and time for administration for infusion.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in **Section 3.1.**

Any overdose or incorrect administration of any of the study treatments should be noted in the patient's medical records. Adverse events associated with an overdose or incorrect administration of any of the study treatments should be recorded in the patient's medical records.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in **Section 6.2.**

4.3.2.1 Ipatasertib

Ipatasertib will be administered at the starting dose of 400mg or 300mg (depending on dosing level assignment) orally QD on a continuous dosing for Arms A & B, 1-28 days cycle. For Arm C, ipatasertib starting dose will be 300mg daily, days 1-21 of 28 day cycles. Treatment will continue until the patient experiences disease progression, intolerable toxicity, or withdraws consent (see **Section 3.1** for details).

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 (not taken within 8 hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or vomited doses will not be made up.

A sufficient amount of ipatasertib should be provided to the patient to last one treatment cycle. Patients will be instructed to bring their bottles of ipatasertib and their medication diaries to each study visit.

Study participants are required to document ipatasertib and loperamide or other anti- diarrhea medication usage with a pill diary (**Appendix 9**).

4.3.2.2 Carboplatin

Carboplatin will be given at a starting dose of AUC at 2 on days 1, 8, and 15 every 28 days for **Arm A**. Carboplatin will be given at a starting dose of AUC at 2 on days 1,8,15 of 28 day cycles for **Arm B**. Carboplatin will be administered as an intravenous infusion over 30 minutes, administered after paclitaxel dose.

Carboplatin dose (mg) = AUC X (GFR + 25)
(Calculated total dose is in mg -not mg/m^2)

The Creatinine Clearance (to replace GFR) will be calculated for each treatment course using the Cockcroft-Gault formula (**Appendix 2**):

Note: The serum creatinine level to be used in the following calculations must be $\geqslant$ 0.7 mg/dL for patient age <65, if the measured serum creatinine level is < 0.7 mg/dL, use 0.7 mg/dL as the value in this calculation. For patient age $\geq$ 65, if measured serum creatinine is < 0.8 mg/dL, use 0.8 mg/dL as the value in this calculation.

For Females:

$$\text{CrCl} = \frac{(140\text{-age}) \times \text{wt. in kg.} \times 0.85}{72 \times \text{serum creatinine*}}$$

Use calculated creatinine clearance for GFR in Cockcroft-Gault formula.

For Males:

$$\text{CrCl} = \frac{(140\text{-age}) \times \text{wt. in kg.}}{72 \times \text{serum creatinine*}}$$

Use calculated creatinine clearance for GFR in Cockcroft-Gault formula.

Note: Remember to re-calculate the dose for each treatment cycle. The actual body weight should be used for all calculations. If the actual weight is greater than 1.2 times the ideal body weight, use 1.2 times the ideal body weight as the value in this calculation. Serum creatinine will be check on each day of carboplatin dose. Readjust carbo dose if dose changes on days 8 and 15 is greater than 10% per institutional guidelines.

Note: The GFR (calculated by Cockcroft-Gault) used in the Calvert formula to calculate AUC-based dosing should not exceed 125 mL/min under any circumstance. By definition, this results in the following upper limits on the dose to be administered, by AUC target:

AUC target (mg•min/mL)	Maximum carboplatin dose (mg)
2	300
3	450
4	600

5	750
6	900

Refer to FDA package insert for detailed instructions on drug preparation, storage, and administration.

4.3.2.3 Paclitaxel

Paclitaxel will be given at a dose of 80 mg/m2 administered by IV infusion on days 1, 8, and 15 of every 28 day cycles for **ArmA**.

The paclitaxel infusion will be delivered over at least 60 minutes for each dose per institutional guidelines and administered after the oral dose of ipatasertib and before carboplatin dose. Patients should be monitored during paclitaxel administration per institutional policies.

Calculation of body surface area for the purposes of dosing of paclitaxel should be made according to the prescribing information. If the patient's weight changes by >10% during the study, the body surface area and drug doses should be recalculated.

Patients may receive anti-emetic and other prophylactic treatments, according to institutional practice.

Refer to FDA package insert for detailed instructions on drug preparation, storage, and administration.

If patients develop moderate or severe allergy to paclitaxel despite adequate premedication, weekly nab-paclitaxel can be used to replace weekly paclitaxel following standard institutional practice after discussion with PI.

4.3.2.4 Capecitabine

Capecitabine will be given at a starting dose of 750mg/m2 1 week on, 1 week off every 2 weeks (28 days cycle) for Arm C. Calculation of body surface area for the purposes of dosing of capecitabine should be made according to the prescribing information. If the patient's weight changes by >10% during the study, the body surface area and drug doses should be recalculated.Patients may receive anti-emetic and other prophylactic treatments, according to institutional practice.

Refer to FDA package insert for detailed instructions on drug preparation, storage, and administration.

4.3.2.5 Atezolizumab

Atezolizumab will be given at a dose of 840mg administered by IV infusion on days 1 and 15 of every 28 day cycles for **Arm** C. Refer to FDA package insert for detailed instructions on drug preparation, storage, and administration.

4.3.2.6 Criteria for Starting Subsequent Cycles

All toxicities (except alopecia, fatigue and lymphopenia, cancer-related pain, hypertension, hyperglycemia, hypoalbuminemia, elevated serum alkaline phosphatase, neuropathy) must resolved to ⩽ **grade 2neutropenia and thrombocytopenia** prior to initiation of the next cycle of therapy. Qualifying laboratory tests and procedures can be obtained up to 72 hours before planned initiation of therapy from the 2nd cycle onwards.

4.3.2.7 Dose Interruption, Dose Delays and Dose Modification

For criteria of dose interruption, dose delay and dose modification, please refer to **Section 5.1.5: Management of Patients Who Experience Adverse Events**.

For all arms, if ipatasertib dose is held due to toxicity, make-up dose will not be given.

For both Arm A and Arm B, if the infusion dose on Day 1, 8, or 15 is missed due to toxicity, make-up dose will not be given.

If patient encounters dose delays, timing of restaging scans will be determined by treatment cycles, not by total weeks on study.

4.3.2.8 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see **section 4.5** and **Appendix 1**.

Management of atezolizumab specific adverse events: Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Investigators are encouraged to review and refer to Clinical Practice Guidelines for management of immune-related adverse events in patients treated with immune checkpoint inhibitors published by the American Society for Clinical Oncology (Brahmer 2018) and the European Society for Medical Oncology (Haanen 2017), along with the dose modification guidelines provided in this protocol for evaluation and management of potential immune adverse events. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. More severe immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. Management of patients with Grade 3 or 4 atezolizumab related immune toxicities will require aggressive immunosuppressive therapies. For details, refer to section 5.1.5.7.11.

4.3.3 Other Treatments: Premedications and Prophylactic Treatment

Because of the known potential for allergic reactions to paclitaxel and/or the

Cremophor® vehicle or carboplatin, precautions must be taken to decrease the risk of anaphylaxis. Patients must be premedicated prior to paclitaxel with dexamethasone, diphenhydramine, and an H2-receptor blocker (i.e., ranitidine or famotidine) or per institutional practice. H2-receptor antagonists, such as **cimetidine**, which are known to inhibit cytochrome P450, are **excluded**.

Steroid use may potentiate hyperglycemia, which can also be induced by ipatasertib**.**
For ⩾ Grade 2 hyperglycemia (fasting glucose 160-250)**, STAT endocrinology consult should be arranged by treating physician in 24h**.

Diarrhea is a common adverse event associated with ipatasertib and/or paclitaxel treatment. In this current study, to improve diarrhea management and patient experiences, loperamide (2 mg twice a day or 4 mg once a day) will be administered daily as prophylaxis for diarrhea in the first cycle if allowed by local guidance. If side effects of loperamide are not tolerated, doses may be reduced at any time. Investigators are encouraged to continue this dosing for the remainder of the study using their discretion based on clinical judgments. **If loperamide is ineffective in controlling diarrhea, other agents such as lomotil (diphenoxylate/atropine) and or colestipol can be used per discretion of treating physician.**

Study participants are required to document their diet, bowel movement and anti-diarrheal medication usage (**Appendix 8**).

If diarrhea occurs, it should be managed per guidelines in **Table 5, page 65**; upon resolution or when study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments.

4.3.4 Investigational Medicinal Product (IMP) Accountability

Investigational Medicinal Product (IMP), specifically ipatasertib required for completion of this study, will be provided by Roche.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure, or will be returned to the Sponsor with the appropriate documentation.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.5 Continued Access to Ipatasertib

The Industry sponsor will offer continued access to sponsor study drug (ipatasertib) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Sponsor study drug (ipatasertib) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Sponsor study drug (ipatasertib) after completing the study if any of the following conditions are met:

- The Sponsor study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for breast cancer
- The Sponsor has reasonable safety concerns regarding the drug as treatment for breast cancer
- Provision of the drug is not permitted under the laws and regulations of the patient's Country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:
http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study treatment to the treatment discontinuation visit. All such medications should be reported to the investigator and recorded in the patient's medical records.

4.4.1 Permitted Therapy and Supportive Care

Patients are permitted to use the following therapies during the study:

- Oral contraceptives, as allowed per local guidelines
- Palliative radiotherapy (e.g., treatment of known bony metastases or symptomatic relief of pain) as outlined below:

  Palliative radiotherapy is permitted for a preexisting lesion, provided it does not interfere with the assessment of tumor target lesions (e.g., the lesion to be irradiated must not be a site of measurable disease). Study treatment should be suspended during palliative radiotherapy (see **Section 4.4.3**)

- Premedication with antihistamines, antipyretics, and/or analgesics for each paclitaxel administration
- **Prophylactic use of loperamide is mandated in the first cycle, and as clinically indicated in subsequent cycles to prevent diarrhea.** Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in **Section 5.1.5.7**; please refer to that section for additional details. Patients should be educated/reminded to be cognizant of the onset, duration, severity, and frequency of symptoms and the medications administered.
- Granulocyte colony-stimulating factor treatment is permitted for patients receiving paclitaxel or carboplatin/paclitaxel arm. The primary prophylaxis should be administered per the ASCO, EORTC, and European Society for Medical Oncology (ESMO) guidelines; namely, in patients who are ≥60 years of age and/or with comorbidities (Smith *et al.* 2006; Aapro *et al.* 2011).
- Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zolendronic acid and denosumab) used specifically to prevent skeletal events (e.g., bone metastasis, osteoporosis) is allowed.
- Luteinizing hormone-releasing hormone (LHRH) agonists for ovarian function preservation are allowed.
- Patients who have type I or type II diabetes mellitus must be followed by an endocrinologist when on study.

In general, investigators/treating physicians should manage a patient's care with supportive therapies as clinically indicated and per institutional practice. For example, patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per institutional practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Systemic corticosteroids are recommended, at the discretion of the investigator, for the treatment of specific immune-related adverse events when associated with atezolizumab (refer to the Atezolizumab Investigator's Brochure for details). Atezolizumab should be temporarily held during systemic corticosteroids treatment.

For usage of antiemetics and treatment for neuropathy, physicians are advised to follow ASCO and/or NCCN guidelines, as appropriate.

4.4.2 Cautionary Therapy for Ipatasertib

Patients who require radiation or surgery as part of medical treatment in the absence of radiographic disease progression must exercise caution, and all study treatment should be

temporarily held for at least 7 days before and after the procedure (at least 14 days after radiation is recommended). After the temporary treatment hold is complete, study treatment

In vitro data suggest that ipatasertib is metabolized by CYP3A and may be a time-dependent inhibitor of CYP3A4. A clinical drug–drug interaction study with midazolam (a sensitive CYP3A substrate) showed a 2.2-fold increase in midazolam exposures in presence of steady-state Ipatasertib dosed at 600 mg QD. Therefore, sensitive CYP3A substrates with narrow therapeutic window should be avoided. Given that ipatasertib is primarily metabolized by CYP3A, there is a high potential for drug–drug interactions of ipatasertib with any medication that strongly inhibits or induces CYP3A. Data from a clinical study showed that ipatasertib exposures were reduced by approximately 50% when co-administered with enzalutamide, a strong CYP3A inducer. Strong CYP3A inhibitors are expected to increase ipatasertib exposures significantly.

Therefore, the following drugs should be avoided or used with caution.

- Strong CYP3A4/5 inhibitors, such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, voriconazole, and/or grapefruit juice
- Strong CYP3A4/5 inducers, such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort or hyperforin
- CYP3A4/5 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
- **Paclitaxel exposures may be increased due to CYP2C8 inhibition; therefore, strong and moderate CYP2C8 inhibitors, such as gemfibrozil, teriflunomide, clopidogrel, and deferasirox should be used with caution during treatment with paclitaxel. Similarly, CYP2C8 inducers should be avoided or used with caution.**
- Patients who require short-term use of a strong CYP3A4/5 inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (i.e., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least 5 half-lives or 7 days after the last dose of these drugs.
- **Patients are permitted to take moderate inhibitors of CYP3A4 with caution.**

Patients should be closely monitored. Refer to the following information for further guidance on CYP450–drug interactions and a list of common substrates, inhibitors, and inducers:

> Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (U.S. Food and Drug Administration [FDA]): https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Herbal Therapies:

Concomitant use of herbal therapies is prohibited because their pharmacokinetics,

safety profiles, and potential drug-drug interactions are generally unknown.

4.4.3 Cautionary Therapy for Capecitabine (Arm C)

Anticoagulants: Anticoagulants Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several months after initiating capecitabine therapy and, in a few cases, within 1 month after stopping capecitabine. These events occurred in patients with and without liver metastases. In a drug interaction study with single-dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin: The level of phenytoin should be carefully monitored in patients taking capecitabine and phenytoin dose may need to be reduced. Some patients receiving capecitabine and phenytoin had toxicity associated with elevated phenytoin levels. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine and/or its metabolites.

CYP2C9 substrates Other than warfarin, no formal drug-drug interaction studies between capecitabine and other CYP2C9 substrates have been conducted. Care should be exercised when capecitabine is coadministered with CYP2C9 substrates.

Drug-Food Interaction: Food was shown to reduce both the rate and extent of absorption of capecitabine. In all clinical trials, patients were instructed to administer capecitabine within 30 minutes after a meal. It is recommended that capecitabine be administered with food.

4.4.4 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below for ipatasertib.

- Investigational therapy (other than protocol-mandated study treatment) is prohibited within 14 days prior to initiation of study treatment and during study treatment.
- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy) is prohibited for various time periods prior to starting study treatment, depending on the agent (see **Section 4.1.2**), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy and local therapy under certain circumstances (see **Section 4.4.1** for details for details).
- Chronic use of a strong CYP3A4/5 inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible after enrollment (refer to the guidance in **Section 4.4.2.1**)
- Live, attenuated vaccines (e.g., FluMist®) are prohibited within 28 days prior to start of treatment, during study treatment, and for 5 months after the last dose of study treatment

- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 28 days or 5 half-lives of the drug, whichever is longer, prior to start of treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab.
- Systemic immunosuppressive medications (including, but not limited to, azathioprine, methotrexate, and thalidomide) are prohibited during study treatment because these agents could potentially alter the efficacy and safety of atezolizumab.
- Steroids greater than or equivalent of 10 mg prednisone/day is contraindicated.

4.4.5 Prohibited Food

Use of the following foods is prohibited as described below:

- Consumption of grapefruit juice, a potent CYP3A4 enzyme inhibitor, is prohibited during the study treatment period and for 10 days after the last dose of study treatment.
- Consumption of St. John's wort, a potent CYP3A4 enzyme inducer, is prohibited for up to 14 days prior to and during the study treatment period, and for 10 days after the last dose of study treatment.

4.4.6 Additional Restrictions

No food or fluids other than water will be allowed for 8 hours prior to each Day 1 study visit until after study laboratory samples for fasting glucose and fasting lipid profile, as applicable, are obtained (see **Appendix 1 Study Calendar**).

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Study calendar. All activities must be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Voluntary, written, dated, and signed informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations or submission of archival tissues). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened, and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 14 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Further, to assess the actual intake of anti-diarrheal medication use, patients will complete a medication diary each day. Patients will receive the diary on the first day of each cycle, with site staff completing information on any prescribed anti-diarrheal medications, including the recommended dosage and route of administration. Patients should use the diary to record daily ipatasertib dosing and specifically any anti-diarrheal medications used (prescribed or over-the-counter) taken on that cycle of treatment. The intake of antidiarrheal medication will be reported in eCRF. Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.3 Physical Examinations

A complete physical examination, performed at screening and other specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Any abnormality identified at baseline should be recorded in the General Medical History and Baseline Conditions eCRF.

Limited, symptom-directed physical examinations should be performed at specified post-baseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position after resting for at least 5 minutes, respiratory rate and oral, axillary or tympanic temperature.

On paclitaxel dosing days, vital signs should be recorded prior to dosing and at the end of the infusion.

4.5.5 Tumor and Response Evaluations

Patients will undergo tumor assessments with CT scan (with oral and IV contrast) of chest, abdomen, pelvis and bone scan of at baseline, every **3 cycles(12 weeks) (bone scan only if indicated)** following treatment initiation regardless of dose delays, until radiographic disease progression per RECIST v1.1 or loss of clinical benefit as determined by the investigator (see **Section 3.1** for details). Protocol specific procedures will not be completed on

patients who are no longer on the study.

All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and within 35 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include CT scans (with oral or IV contrast) of chest, abdomen, pelvis, bone scan and MRI of brain with contrast. If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed**. MRI scan of the brain must be done at screening to evaluate CNS metastasis in all patients (CT brain with contrast can be performed if MRI is contraindicated).** At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used.

If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

Response will be assessed by the study radiologist using RECIST v1.1 (see **Appendix 6**). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Results must be reviewed by the investigator before dosing at the next cycle.

An objective response should be confirmed by repeat assessments ≥4 weeks after initial documentation. At the investigator's discretion, and if clinically indicated, CT scans may be repeated at any time if progressive disease is suspected, and other methods of assessment of measurable disease may be used (e.g., brain scans using CT or MRI) in addition to those listed above. For symptomatic deterioration attributed to disease progression, every effort should be made to document progression through use of objective criteria per RECIST v1.1.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Laboratory samples should be drawn according to the study calendar (see **Appendix 1**) and within 48 hour prior to study drug administration.

The following tests are required for Day 1 dosing for every cycle: CBC, differential; Comprehensive metabolic panel including glucose, creatinine, potassium, calcium, total bilirubin, ALP (total ALP), AST, ALT. Amylase, lipase, and thyroid test every other cycle.

Screening local laboratory assessments obtained within 96 hours before C1D1 do not have to be repeated for C1D1.

Screening labs include:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Chemistry panel (serum or plasma): sodium, potassium, magnesium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total bilirubin, alkaline phosphatase, ALT, AST, LDH
- Coagulation: INR, aPTT
- Fasting lipid profile (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides)
- Glycosylated hemoglobin (HbA1c
- Thyroid function testing: thyroid-stimulating hormone, free triiodothyronine (T3) (or total T3 for sites where free T3 is not performed), and free thyroxine (also known as T4)
- Urinalysis
- Pregnancy test: All women of childbearing potential will have a serum pregnancy test at screening. A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Screening viral serology: HBsAg, total hepatitis B core antibody (HBcAb), HCV antibody; additional tests for HBV DNA or HCV RNA will be required to confirm eligibility in patients with a positive antibody result.
- HIV serology: HIV-1/2 antibody
- Correlative Peripheral Blood sample such as plasma or PBMC will be collected for exploratory research on biomarkers at baseline, C2D1, C4D1and end-of-treatment visit.
- Plasma Calprotectin will be collected at baseline, C2D1, C4D1 and end-of-treatment visit.
- Stool microbiome will be collected at baseline, C4D1 and end-of-treatment visit.
- Archival or newly collected tumor tissue sample obtained at baseline for determination of PIK3CA/AKT1/PTEN status and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of 30% tumor volume that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (**at least three 18 gauge cores, embedded in a single paraffin block**), or excisional, incisional, punch, or forceps biopsy are acceptable. **Fine-needle aspiration** (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell

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pellets from pleural effusion, and lavage samples **are not acceptable**. **Tumor tissue from bone metastases that have been decalcified are not acceptable.**

If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. *Patient should be encouraged to have* *repeat tumor biopsy at time of progression**, if deemed clinically feasible, for exploratory research on biomarkers and study of potential molecular mechanisms of resistance.***

Biopsies at the time of progression should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. Samples collected via resection, core-needle biopsy (at least **three 18 gauge needle cores** preferred), or excisional, incisional, punch, or forceps biopsy are acceptable.

Exploratory biomarker research may include, but will not be limited to:

- Somatic mutations and copy-number variations by NGS or PCR-based methods in tumor tissue and ctDNA
- Expression analysis (e.g., RNA-Seq) of genes related to PI3K/Akt pathway activity, immune infiltration/activation, apoptosis, and breast cancer biology (i.e., intrinsic subtypes)
- Immunohistochemistry-based analysis or quantitative digital immunohistochemistry of tumor suppressors, such as PTEN, and markers of immune infiltration and activation, such as CD8 and PD-L1

NGS may be performed by Foundation Medicine or other NGS platform. If performed by Foundation Medicine or other CLIA-certified NGS platform, the investigator can obtain results from these analyses in the form of an NGS report. If allowed by local IRB, the investigator may share and discuss the results with the patient if the assay is CLIA-certified, unless the patient chooses otherwise. Results may not be available for samples that do not meet testing criteria.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples.

Given the complexity and exploratory nature of the analyses, data derived from whole genome sequencing (WGS), whole exome sequencing (WES) or partial exome sequencing (PES) of specimens will generally not be provided to patients.

Electrocardiograms and echocardiogram

An ECG and echocardiogram is required at screening and when clinically indicated. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented in the patient’s medical records.

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4.5.7 Patient-Reported Outcomes

To more fully characterize the clinical profile of ipatasertib, PRO data will be obtained through use of the following questionnaires: European Organization for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire for cancer (EORTC QLQ-C30). The questionnaires will be translated as appropriate into the local language.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment.

Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30 questionnaire at each tumor assessment visit until radiographic disease progression per RECIST v1.1.

All patients will complete the EORTC QLQ-C30 questionnaire at 3 and 6 months after radiographic disease progression per RECIST v1.1.

4.5.7.1 *EORTC QLQ-C30*

The EORTC QLQ-C30 is a validated, reliable self-report measure (Aaronson *et al*. 1993; Fitzsimmons *et al*. 1999) (see **Appendix 11**). It consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, pain), global health/quality of life, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week. Scale scores can be obtained for the multi-item scales.
The EORTC QLQ-C30 module takes approximately 10 minutes to complete.

4.5.8 Mandatory Samples for Circulating Tumor DNA

Blood sampled will be collected for DNA extraction to enable whole genome sequencing (WGS), whole exome sequencing (WES) or partial exome sequencing (PES) to identify germline mutations and/or somatic mutations that are predictive of response to study drug, are associated with progression to a more severe disease state, are associated with acquired resistance to study drug, are associated with susceptibility to developing adverse events, or can increase the knowledge and understanding of disease biology. The blood samples may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and WES provides a comprehensive characterization of the exome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see Section 8 & and **Appendix 10**.

Blood samples collected for WGS/WES/PES are to be stored until they are no longer needed or until they are exhausted.

Patient medical information associated with WGS/WES/PES specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient.

Given the complexity and exploratory nature of the circulating tumor DNA and WGS/WES/PES analyses, data derived from these analyses will generally not be provided to patients.

4.5.9 Post-Treatment Follow-Up

All participants will enter follow-up after completing End-of-Treatment assessments. This is comprised of:

- **Safety Follow-up**- 30 days post-last dose of protocol therapy.
- **Note** the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Response Follow-up**- for those who have yet to have disease progression.
- **Survival Follow-up**- for all participants who have progressed OR completed Active Response Follow-Up.
- Assessment timepoints and windows are detailed in **Appendix 1** Study Calendar.

At post-treatment follow-up visits, survival follow-up information, subsequent treatment and outcome, and PROs will be collected via telephone calls, patient's medical records, and/or clinic visits approximately every 3 months until death, loss to follow-up, or study termination by Sponsor. All patients will be followed for post-treatment follow-up information unless the patient requests to be withdrawn from study post-treatment follow-up; this request must be documented in the source file and signed by the investigator.

For patients who discontinue treatment without evidence of disease progression per RECIST v1.1, in addition to post-treatment follow-up, patients will be followed every 12 weeks for tumor assessments (disease follow-up clinic visits; see Study Calendar **Appendix 1**) until documented progression per RECIST v1.1, elective withdrawal from the study, or study completion or termination.

4.6 DURATION OF THERAPY, CRITERIA OF REMOVAL FROM STUDY, PATIENT, AND STUDY DISCONTINUATION

Patients must permanently discontinue study treatment (ipatasertib and carboplatin or carboplatin/paclitaxel) if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment

- Investigator or Sponsor determines it is in the best interest of the patient
- Withdrawal of consent from the study treatment
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Disease progression per investigator's assessment according to RECIST v1.1 or symptomatic deterioration attributed to disease progression

The primary reason for study treatment discontinuation should be documented in the patient's medical records.

Patients will return to the clinic for a treatment discontinuation visit ≤30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will continue to undergo tumor response assessments and PRO assessments as outlined in the schedule of activities (see **Appendix 1**).

After treatment discontinuation, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months until death (unless the patient withdraws consent or the Investigator terminates the study*).*

4.6.1 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. Patient will remain treatment on the study unless at least one of the following criteria was met:

- Confirmed disease progression
- Completed protocol therapy
- Completion of study activities (treatment and overall survival follow-up after protocol treatment)
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
    - **Note:** If one agent is discontinued due to toxicity, then the participant may continue to receive the other study agents
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the Investigator
- Investigator or Sponsor determines it is in the best interest of the patient

- Withdrawal of consent for further protocol therapy (Refer to Withdrawal Section from Ethical Considerations)
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to End of Treatment assessments, and then to follow-up (**Section 4.3**).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF. The COH DCC and the Study PI should be promptly notified of the change in participant status.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented in the patient's medical records. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study prematurely will be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.2 Study Discontinuation

The Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF. The COH DCC should be promptly notified of the change in participant status.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Ipatasertib is not currently approved for any indication, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with ipatasertib in completed and ongoing studies.

The anticipated important safety risks and management plan for ipatasertib and paclitaxel are outlined below. The identified risks associated with ipatasertib treatment include gastrointestinal toxicities (diarrhea, nausea, vomiting, and oral mucositis), fatigue/asthenia, erythema multiforma, rash, and hyperglycemia. Refer to the Ipatasertib Investigator's

Brochure for a complete summary of safety information of ipatasertib as a single-agent and in combination with chemotherapy and other anticancer therapies. Refer to the Carboplatin and Paclitaxel Prescribing Information or Summary of Product Characteristics for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including investigator's assessment of the nature, frequency, and severity of adverse events, as well as expedited reporting of protocol-defined adverse events of special interest regardless of seriousness. Vital signs and relevant laboratory values will be monitored at baseline and during the study.

Guidelines for managing adverse events, including prophylaxis (for diarrhea), and criteria for dose modification (interruption, dose reduction or discontinuation) for the management of specific adverse events attributable to ipatasertib, paclitaxel and carboplatin are summarized in **Section 5**.

Suggested dose reductions for ipatasertib, carboplatin and paclitaxel are listed in **rm A** and **Arm B**. General guidelines for dose modification are provided in **Table 1, 2, 3 & 4.**
COH DSMC will be used during this study for toxicity monitoring. For details, refer to **Section 6**: **Data & Safety Monitoring Plan, Adverse Event and Unanticipated Problem Reporting**

5.1.1 Risks Associated with Ipatasertib in Combination with Paclitaxel

Ipatasertib in combination with paclitaxel was administered to 61 cancer patients in Study GO29227 (LOTUS). Adverse events related to ipatasertib/placebo whose incidences were higher by ⩾10% in patients receiving ipatasertib + paclitaxel versus placebo + paclitaxel were diarrhea (88.5% vs. 16.1%) and nausea (41.0% vs. 19.4%). The most frequent Grade ⩾3 adverse events (reported in ⩾ 5% of patients in either treatment arm) in patients in the ipatasertib + paclitaxel arm vs. placebo + paclitaxel arm were diarrhea (14 patients [23.0%], all Grade 3, vs. 0 patients), neutropenia (6 patients [9.8%] vs. 1 patient [1.6%]), decreased neutrophil count (5 patients [8.2%] vs. 4 patients [6.5%]), and fatigue (2 patients [3.3 %] vs. 4 patients [6.5%]), respectively.

The incidence of overall neutropenia in the LOTUS Study was similar in both arms (34% in the ipatasertib + paclitaxel arm vs. 39% in the placebo +paclitaxel arm), but Grade ⩾3 neutropenia, analyzed by grouped terms of similar medical concept, was higher in the ipatasertib + paclitaxel arm (18% vs. 8%). Thus, for recurrent Grade ⩾ 3 neutropenia, ipatasertib should be reduced by one dose level when treatment is restarted (refer to the Adverse Events Management Guidelines in **Section 5.1.5.7**).

Refer to the Ipatasertib Investigator's Brochure for further information regarding the nonclinical and clinical safety evaluation of ipatasertib as a single agent and in combination with chemotherapy.

5.1.2 Risks Associated with Ipatasertib

Hyperglycemia, including cases of Grade 3 or Grade 4 hyperglycemia, has been reported in patients receiving ipatasertib as monotherapy or ipatasertib in combination with other anticancer drugs or hormonal therapy. Hyperglycemia of any grade, regardless of causality, was reported in 35.3% of patients who received ipatasertib as a single agent in the Phase I Study PAM4743g, with Grade 3 hyperglycemia occurring in 1 patient (2.0%). In the GO27983 study, hyperglycemia of any grade, regardless of causality, was reported in 22.6%, 9.1%, and 7.4% of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, respectively. Grade 3 hyperglycemia occurred in 10.7%, 2.3%, and 2.5% of patients in the 400 mg, 200 mg, and placebo arms, respectively. One patient (1.2%) in the ipatasertib 400 mg arm experienced Grade 4 hyperglycemia. There were no other instances of Grade 4 or higher hyperglycemia events in any arm. In the GO29227 study, hyperglycemia of any grade, regardless of causality, was reported in 9.5% and 3.3% of patients in the ipatasertib 400 mg and placebo arms, respectively. There were no reports of Grade ≥3 hyperglycemia.

GI toxicities such as nausea, vomiting, diarrhea, and stomatitis/oral mucositis have been commonly observed in patients receiving ipatasertib as monotherapy or in combination with other anticancer drugs.GI toxicities of any grade, regardless of causality, were commonly reported in patients who received ipatasertib as a single agent in the Phase I Study PAM4743g, including nausea (78.4%), diarrhea (72.5%), vomiting (58.8%), and stomatitis or mucosal inflammation (7.8%). In this study, the reported Grade 3 GI toxicities included diarrhea (7.8%), and nausea (2.0%). In the GO27983 study, GI toxicities, irrespective of grade or causality (presented by proportion of patients affected in the ipatasertib 400 mg, ipatasertib 200 mg, and placebo arms, respectively), included diarrhea (77.4%, 48.9%, and 24.7%), nausea (53.6%, 35.2%, and 24.7%), vomiting (32.1%, 27.3%, and 14.8%), and oral mucositis (6.0%, 3.4%, and 1.2%). The only Grade 3 GI AEs that affected ≥ 2 patients, irrespective of causality, were diarrhea (13.1%, 2.3%, and 1.2%) and nausea (2.4%, 0%, and 0%). There were no Grade 4 or 5 events in this category in this study. In the GO29227 study, GI toxicities of any grade, regardless of causality, reported in the ipatasertib 400 mg and placebo arms, respectively, included diarrhea (92.1% and 20.0%), nausea (52.4% and 33.3%), vomiting (27.0% and 23.3%), and oral mucositis (23.8% and 15.0%). Grade 3 diarrhea occurred in 22.2% of the ipatasertib 400 mg arm and 0% of the placebo arm. Grade 3 vomiting was reported in 3.2% and 0% of the ipatasertib 400 mg and placebo arms, respectively. With regard to Grade 3 nausea and Grade 3 oral mucositis, there was 1 patient in each arm (1.6% and 1.7% in the ipatasertib 400 mg and placebo arms, respectively). There were no Grade 4 or Grade 5 diarrhea, nausea, vomiting, or oral mucositis events in any arm.

Rash, primarily manifested as maculopapular type with or without pruritus, has been commonly reported in patients receiving treatment with ipatasertib. Rash-related events of any grade, regardless of causality, were reported in 15.7% of patients who received ipatasertib as a single agent in the Phase I Study PAM4743g; Grade 3 rash (toxic skin eruption as reported term) was reported in 1 patient (2.0%). In the GO27983 study, irrespective of grade or causality, the proportion of patients experiencing a rash-related event was 23.8%, 9.1%, and 6.2% in the

ipatasertib 400 mg, ipatasertib 200 mg, and placebo arms, respectively. Of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, 9.5%, 2.3%, and 0%, experienced Grade 3 rash, respectively. One patient (1.2%) in the ipatasertib 400 mg arm experienced a Grade 4 event. There were no other instances of Grade ≥4 events in this study. In the GO29227 study, rash of any grade, regardless of causality, was reported in 30.2% and 30.0% of the ipatasertib 400 mg and placebo arms, respectively. There was 1 patient with Grade 3 rash in each arm (1.6% and 1.7% in the ipatasertib 400 mg and placebo arms, respectively). There were no cases of Grade 4 or Grade 5 rash events in any arm. Cases of Grade 3 rash requiring dose interruption and treatment with topical or systemic corticosteroids have also been observed from other ongoing ipatasertib studies. In addition, cases of erythema multiforma have been identified,

Fatigue or asthenia of any grade, regardless of causality, has been observed in 62.7% of patients receiving ipatasertib as a single agent in the Phase I Study PAM4743g, with 5 (9.8%) cases of Grade 3 asthenia/fatigue reported. In the GO27983 study, asthenia/fatigue of any grade, irrespective of causality, was reported in 48.8%, 45.5%, and 43.2% of patients in the ipatasertib 400 mg, 200 mg, and placebo arms, respectively. Grade 3 asthenia/fatigue occurred in 9.5%, 5.7%, and 3.7% of patients, respectively, as above. There were no cases of Grade 4 or Grade 5 asthenia/fatigue events in any arm. In the GO29227 study, asthenia/fatigue of any grade, regardless of causality, was reported in 49.2% and 43.3% of the ipatasertib 400 mg and placebo arms, respectively. Grade 3 asthenia/fatigue was reported in 6.3% and 6.7% of the ipatasertib 400 mg and placebo arms, respectively. There were no cases of Grade 4 or Grade 5 asthenia/fatigue events in any arm.

Refer to the Ipatasertib Investigator's Brochure for further information regarding the nonclinical and clinical safety evaluation of ipatasertib as a single agent and in combination with chemotherapy.

5.1.3 Risks Associated with Paclitaxel or Carboplatin for Arm A and B

Risks Associated with Paclitaxel:
In prior clinical trials of paclitaxel, the following safety signals associated with paclitaxel were identified: nausea, vomiting, diarrhea, stomatitis, peripheral neuropathy, hypersensitivity reactions, and hematologic toxicity.

To be eligible for the current study, patients must have adequate hematologic function, as manifested by measurements of complete blood cell counts. Furthermore, blood cells will be assessed prior to each treatment cycle.

Adverse events related to paclitaxel in the LOTUS study (GO29227) whose incidences were higher by≥10% in patients receiving ipatasertib + paclitaxel versus placebo + paclitaxel were diarrhea (78.7% vs. 12.9%), nausea (41.0% vs. 24.2%), and peripheral sensory neuropathy (26.2% vs. 16.1%).

Patients will be monitored for other paclitaxel-associated adverse events as outlined in

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this section. For more details regarding the safety profile of paclitaxel, see the Paclitaxel Prescribing Information or Summary of Product Characteristics.

Risks Associated with Carboplatin:
In prior clinical trials of carboplatin, the following safety signals associated with carboplatin were identified: nausea (10-15%), vomiting (65-81%), neutropenia (67%), anemia (71-90%), thrombocytopenia (62%) and hypersensitivity reactions (2-16%).

Patients will be monitored for other carboplatin-associated adverse events as outlined in this section. For more details regarding the safety profile of carboplatin, see the carboplatin Prescribing Information or Summary of Product Characteristics.

5.1.4 Risks Associated with Capecitabine and Atezolizumab for Arm C

Risks Associated with Capecitabine:
In prior clinical trials of capecitabine, the following safety signals associated with capecitabine were identified: hand-foot syndrome, diarrhea, nausea, vomiting, and fatigue. In studies of capecitabine as single agent in patients with metastatic breast cancer, patients received 21-day cycles of oral capecitabine 1250 mg/m^2 twice daily for 14 days followed by a 7-day rest period. The most common (>20% patients) treatment-related adverse events were Lymphopenia (94%), Anemia (72%), hand–foot syndrome (57%), diarrhea (57%), nausea (53%), Fatigue (41), vomiting (37%), Dermatitis (37%), neutropenia (26%), Paresthesia (21%), Thrombocytopenia (24%), stomatitis (24%), Anorexia (23%), Hyperbilirubinemia (22%) and Abdominal Pain (20%). Most treatment-related adverse events were mild to moderate in intensity, and the only grade 3/4 adverse events occurring in more than 5% of patients were lymphopenia (44% grade 3; 15% grade 4), hyperbilirubinemia (9% grade 3; 2% grade 4), hand–foot syndrome (11%, grade 3 only), diarrhea (12% grade 3; 3% grade 4), fatigue (8%, grade 3 only), and stomatitis (7%, grade 3 only).For more details regarding the safety profile of capecitabine, see the capecitabine prescribing information.

Risks Associated with Atezolizumab:
Atezolizumab has been associated with risks such as the following: IRRs and immune-mediated hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, and myositis. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Refer to Section 6 of the Atezolizumab Investigator's Brochure for a detailed description of anticipated safety risks for atezolizumab.

5.1.5 Management of Patients Who Experience Adverse Events

5.1.5.1 Definition of Dose-Limiting Toxicities (DLT)

A dose-limiting toxicity (DLT) is defined as one of the following Adverse Events (AEs), occurring in **the first 4 weeks** of the study if considered to be definitely, probably, or possibly related to treatment.

The following define a DLT:

- Hy's law
- Grade 3 or 4 non-hematologic toxicity according to the NCI CTCAE Version 5.0, except for skin toxicity, alopecia, nausea, vomiting, diarrhea (see below).
- For patients with ≤ Grade 2 hepatic transaminase levels at baseline as a result of liver metastases, AST or ALT level > 8 x ULN or AST or ALT >5x ULN for ≥14 days
- For patients without baseline liver metastases, AST or ALT level > 5 x ULN
- Grade ≥3 nausea, vomiting, or diarrhea that persists more than 3 days despite maximal supportive intervention.
- Grade 3 thrombocytopenia with bleeding requiring transfusion, or Grade 4 thrombocytopenia with or without bleeding more than 7 days.
- Grade 4 neutropenia that persists more than 7 days.
- Grade 3 or 4 neutropenia with fever, defined as single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour.
- Grade 3 or 4 electrolyte abnormality that lasts >72 hours
- Grade 3 or 4 electrolyte abnormality that lasts ≤ 72 hours and patients are symptomatic
- Grade 3+ amylase or lipase elevation NOT associated with symptoms or clinical manifestations of pancreatitis does not need to be counted as a DLT.
- Grade ≥3 skin toxicity despite best supportive care, with exception of Grade 3 rash that resolves to Grade ≤2 within 14 days with appropriate supportive therapy. If a total at least 75% of the planned dose of ipatasertib cannot be administered in the first cycle due to toxicity or more than one dose of either paclitaxel or carboplatin is missed due to toxicity. Prolonged delay (>2 weeks) in initiating cycle 2 due to treatment-related toxicity.
- Grade ≥3 fatigue that lasted ≥1 week
- Any death not clearly due to the underlying disease or extraneous causes.
- All other Grade ≥ 3 AEs except those that are clearly and incontrovertibly due to disease progression or extraneous causes.

Per statistical design, Arm A, B, and C dosing schedules will be used with detailed dosing levels depicted in **Table A** ,**Table B, and Table C.** There is no intra-patient dose escalation for any arm.

Table A. Arm A levels

Arm A Levels	Ipatasertib (oral)	Carboplatin/Paclitaxel
1	400mg po daily	Carboplatin AUC 2 Paclitaxel 80 mg/m2, days 1, 8, 15 every 4 weeks
-1A‡	400mg po daily	Carboplatin AUC 1.5, Paclitaxel 65 mg/m2, days 1, 8, 15 every 4 weeks
-1B†	300 mg po daily	Carboplatin AUC 2, Paclitaxel 80 mg/m2, days 1, 8, 15 every 4 weeks
-1C*	300 mg po daily	Carboplatin AUC 1.5, days 1, 8, 15, Paclitaxel 65 mg/m2, days 1, 8, 15 every 4 weeks
-1D**	300mg po daily	Carboplatin AUC 1.5, days 1, 15 Paclitaxel 65 mg/m2, days 1, 15 every 4 weeks

‡ Dose reduction to level -1A if DLT is attributed to carboplatin/paclitaxel (such as myelosuppression, neuropathy, intolerance to carboplatin/paclitaxel infusion reaction)
†Dose reduction to level -1B if DLT is attributed ipatasertib (such as diarrhea, hyperglycemia)
*Dose reduction to level -1C if DLT and other high-grade toxicities relate to both carboplatin/paclitaxel and ipatasertib, or if levels -1A or -1B are not well-tolerated (e.g. >1 DLT in 6 patients).
**Dose reduction to level -1D if DLT on level 1C.

Table B. Arm B levels

Arm B Levels	Ipatasertib (oral)	Carboplatin
1	400mg po daily	AUC 2 on days 1, 8, 15 every 28 days
-1A‡	400 mg po daily	AUC 1.5 on days 1, 8, 15 every 28 days
-1B†	300 mg po daily	AUC 2 on days 1, 8, 15 every 28 days
-1C*	300mg po daily	AUC 1.5 on days 1, 8, 15 every 28 days
-1D**	300mg po daily	AUC 1.5 on days 1, 15 every 28 days

‡ Dose reduction to level -1A if DLT is attributed to carboplatin (such as myelosuppression, intolerance to carboplatin infusion reaction)
†Dose reduction to level -1B if DLT is attributed ipatasertib (such as diarrhea, hyperglycemia)
* Dose reduction to level -1C if DLT and other high-grade toxicities relate to both carboplatin/paclitaxel and ipatasertib, or if levels -1A or -1B are not well-tolerated (e.g. >1 DLT in 6 patients).
**Dose reduction to level -1D if DLT on level 1C.

Table C. <u>Arm C</u> levels

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Arm C Levels	Drug Dosage		
	Ipatasertib	Capecitabine	Atezolizumab
Dose Level -1	200 mg daily days 1-21	750 mg/m2 BID, 1 week on 1 week off x 2	840 mg IV d1 and 15
Dose Level 1 (starting dose)	300 mg daily days 1-21	750 mg/m2 BID, 1 week on 1 week off x 2	840 mg IV d 1 and 15
Dose Level 2	400 mg daily days 1-21	750 mg/m2 BID, 1 week on 1 week off x 2	840 mg IV d1 and 15
Dose Level 3	400 mg daily days 1-21	1000 mg/m2 BID, 1 week on 1 week off x 2	840 mg IV d1 and 15

28 days each cycle

5.1.5.2 Dose Modifications

The five agents included in this study (ipatasertib, carboplatin, paclitaxel, capecibabine, atezolizumab) have overlapping and non-overlapping toxicity profiles. Neuropathy is likely attributed to paclitaxel. Nausea, vomiting, myelosuppression and infusion reaction can be attributed by both paclitaxel and carboplatin. Diarrhea and stomatitis can be attributed by ipatasertib, capecitabine and paclitaxel. Premedication such as dexamethasone and ipatasertib can both cause hyperglycemia. Nausea, vomiting and myelosuppression can be contributed by all three agents.

Guidelines for dosage modification and treatment interruption or discontinuation are provided below.

Any dose interruption, dose modification, overdose or incorrect administration of study druges should be noted on the corresponding study drug administration eCRF. All adverse events associated with an overdose or incorrect administration of study druges should be recorded on the Adverse Event log eCRF.

5.1.5.3 Dose Modification General Guidelines

Details in this section can be used as guidance for dose modification. Only the specific dose levels shown should be used (**Table 1, Table 2 , Table 3 and Table 4**).

Reasons for dose modifications (interruption or reduction) and discontinuation, the supportive measures taken, and the outcome will be documented in the patient's chart and recorded in the eCRF. Reasons for not adhering to the following guidance should also be documented in the patient’s chart.

On **day 1** of each cycle of treatment, the general parameters for chemotherapy administration include the following:

- ANC ≥ 1500/μl (≤Gr 1)
- Hemoglobin ≥ 8mg/dL *

- Platelet count ≥ 100,000/μL (≤Gr 1)
- Grade ≤ 2 clinically significant chemotherapy-related gastrointestinal toxicity or neuropathy

On the **day 8 & 15** each cycle of treatment, the general parameters for chemotherapy administration include the following:

- ANC ≥ 1000/μl (≤Gr 2)
- Hemoglobin ≥ 8 mg/dL*
- Platelet count ≥ 75,000/μL(≤Gr 2)
- Grade ≤ 2 clinically significant chemotherapy-related gastrointestinal toxicity or neuropathy

* Transfusion allowed on treatment day to meet the hemoglobin criteria

General guidelines for dosage/schedule modification are summarized as follows:

- If any treatment component is held or delayed, the study cycle day count continues and does not shift except day 1 of each cycle; *i.e., every cycle contains exactly 28 days.*
- If ipatasertib treatment is interrupted during the middle of a cycle, carboplatin or carbo/paclitaxel treatment should continue.
- If day 1 of the cycle is interrupted, *consider delaying* the ipatasertib and chemotherapy treatment concurrently for up to 7 days to maintain the 28 day cycle
- If day 8 or 15 of the cycle is interrupted, no makeup dose of chemotherapy treatment will be given.
- If toxicity causes chemotherapy to be omitted, patient should be seen in one week for lab/adverse events follow up/treatment.
- Once the toxicity has resolved to the required level, study treatment and study procedures will be resumed. No makeup doses of day 8 or day 15 carboplatin/paclitaxel will be given.
- For any concomitant conditions at baseline, dose modifications may apply according to the shift in toxicity grade, if the investigator deems it appropriate. For example, if a patient has Grade 1 asthenia at baseline that increases to Grade 2 during treatment, this change may be considered a shift of one grade and may be treated as Grade 1 toxicity for dose-modification purposes if medically appropriate.
- For toxicities assessed by the investigator to be unrelated to study treatment and unlikely to develop into serious or life-threatening events, treatment may be continued at the same dose without reduction or interruption.
- Dose reductions or interruptions may not be required for anemia (non-hemolytic) if satisfactorily managed by transfusions.
- 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.
- Dose modifications for isolated abnormal hematologic laboratory values will be based on hematologic parameters at the start of a treatment cycle.
- Chemotherapy may be interrupted to manage toxicity**.**

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A dosing gap of up to 4 consecutive weeks (approximately 28 days) is permitted.

Any dose hold for longer than 4 weeks for a treatment-related adverse event will require permanent discontinuation of the attributable treatment component and per specific **Adverse Event Management Guidelines in Section 5.1.5.7**. As applicable, patients should continue treatment either on carboplatin or carboplatin/paclitaxel alone, or may continue treatment with ipatasertib alone after discussing with the principle investigator.

5.1.5.4 Dose Modifications for Carboplatin

For adverse events associated with carboplatin, refer to package insert or summary of product characteristics in **section 5.1**.

Table 1: Guidelines for Management of Patients Who Experience Adverse Events Associated with Carboplatin

Event	Action to Be Taken
General guidance for treatment delays and discontinuation	• When a treatment cycle is delayed because of a toxicity resulting from any component of the regimen, all study treatment should generally be withheld and resumed together to remain synchronized. • If one drug is discontinued, treatment with the other drugs may be continued for patients experiencing clinical benefit as determined by the investigator. • Permanently discontinue study treatment if an adverse event requires treatment to be withheld for > 28 days.
IRRs and anaphylaxis	• Guidelines for management of IRRs are provided in **section 5.1.5.7.9**
Hematologic toxicity	
Grade 2 Neutropenia	• Hold treatment for D1 of each cycle till ANC ⩾ 1.5 • Continue study treatment for Days 8 or 15. • Growth factor can be given
Grade 3 Neutropenia	• Withhold study treatment. • Give supportive treatment. • If event resolves to Grade 2 or better, resume study treatment. • 1st episode, reduce by one dose level see **table 2 & 3** and use G-CSF support • 2nd episode of G3 neutropenia despite adequate use of G-CSF support, discontinue day 15 dose of carboplatin 3rd episode of G3 neutropenia despite adequate use of G-CSF support and dose modification, permanently discontinue carboplatin

Event	Action to Be Taken
Grade 3/4 Febrile Neutropenia Or Grade 4 Neutropenia	• Withhold study treatment. • Give supportive treatment. • 1st episode, reduce AUC by one dose level see **table 2 &3** and use G-CSF support • 2nd episode of G3/4 febrile neutropenia or Grade 4 neutropenia despite adequate use of G-CSF support, discontinue day 8 dose of carboplatin (**table 2 & 3**) • 3rd episode of G3/4 febrile neutropenia or Grade 4 neutropenia despite adequate use of G-CSF support, permanently discontinue carboplatin(**table 2 & 3**)
Grade 2 thrombocytopenia	• Withhold study treatment. • Resume treatment if resolved and meet treatment parameter
Grade 3/4 thrombocytopenia	• Withhold study treatment. • 1st episode, reduce by one AUC dose level **see table 2 & 3** • 2nd episode, discontinue day 8 of carboplatin (**table 2 & 3**) • 3rd episode, permanently discontinue carboplatin(**table 2 & 3**)
Gastrointestinal Toxicity	
Grade ⩾3 Nausea Vomiting	• Withhold study treatment. • Nausea and/or vomiting should be controlled with adequate antiemetic therapy. Prophylactic anti-emetic therapy can be used at the discretion of the treating physician. Patients are encouraged to take plenty of oral fluids. If symptoms persist despite maximal anti-emetic therapy, treatment should be withheld until recovery to ⩽ grade 1
Grade ⩾3 Diarrhea	• Withhold study treatment • Refer to management guideline for diarrhea in separate table • Resume treatment only if symptom recovery to ⩽ grade 1
Other Grade 3/4 Toxicities	For any grade 3 or 4 toxicity not mentioned above, withhold drug until the patient recovers to grade 1 or less toxicity. The treatment should then be resumed at one lower dose level for carboplatin.

IRR = infusion-related reaction.

5.1.5.5 Dose Modifications for Ipatasertib and Carboplatin/Paclitaxel

Patients may hold the ipatasertib for up to 4 consecutive weeks (approximately 28 consecutive days) in order to recover from toxicity or an adverse event related to the study drug. If the ipatasertib is discontinued at any time during the study, patients may have the option of continuing on study with chemotherapy alone.

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 (i.e., doses below 200 mg/day of ipatasertib) will be allowed (see **Table 2**).

To manage carboplatin/paclitaxel-related toxicity, no more than one dose reduction for carboplatin/paclitaxel will be allowed (**Table 3 & 4A**).

For Arm C, capecitabine starting dose will be 750mg/m2 Bid. Patient could receive minimal dose of 500mg/m2 bid if dose not tolerated (**Table 4B**).

Table 2: Dose Modification Table for Continuous Daily Dosing Of Ipatasertib

Dose Level [a]	Ipatasertib (400 mg daily)
Starting dose	400 mg daily
First dose reduction	300 mg daily
Second dose reduction	200 mg daily
Third dose reduction	Not permitted

[a] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.

Table 3: Dose Reductions for Carboplatin/Paclitaxel for Arm A

Dose Level [a]	Carboplatin/Paclitaxel
Starting dose	Carboplatin AUC 2, Paclitaxel 80 mg/m2 days 1, 8, 15
First dose reduction	Carboplatin AUC 1.5, Paclitaxel 65 mg/m2 days 1, 8, 15
Second dose reduction [b]	Carboplatin AUC 1.5, Paclitaxel 65 mg/m2 days 1, 15

[a] If the patient continues to experience specified drug-related adverse events after the dose reduction, the treatment should be discontinued.

[b] If the patient continue to experience specific drug-related adverse events after the dose reduction of carboplatin AUC 1.5, and paclitaxel to 65 mg/m2. Skipping Day 8 dose of carboplatin or paclitaxel or both can be permitted for future cycles at the discretion of investigator. Principle investigator should be notified.

Table 4A: Dose Reductions for Carboplatin for Arm B

Dose Level [a]	Carboplatin
Starting dose	Carboplatin AUC 2, days 1, 8,15
First dose reduction	Carboplatin AUC 1.5, days 1, 8,15
Second dose reduction	Carboplatin AUC 1.5, days 1, 15
Third dose reduction [b]	Not permitted

[a] If the patient continues to experience specified drug-related adverse events after the dose reduction, the treatment should be discontinued.

[b] If the patient continue to experience specific drug-related adverse events after the dose reduction of carboplatin AUC 1.5 days 1, 15, carboplatin should be permanently discontinued and patient may continue single agent ipatasertib. Principle investigator should be notified.

Table 4B: Dose Reductions for Capecitabine for Arm C

Dose Level	Capecitabine
Starting dose	Capecitabine 750mg/m2 BID, 7 days on, 7 days off
First dose reduction	Capecitabine 500mg/m2 BID, 7 days on, 7 days off
Second dose reduction [a]	Not permitted

[a] If the patient continues to experience specified drug-related adverse events after the dose reduction, the treatment should be discontinued and patient may continue ipatasertib and atezolizumab. Principle investigator should be notified.

There is no dose modification for atezolizumab since fixed dose will be given per FDA package insert.

5.1.5.6 Treatment Interruption

Treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. **If treatment has been withheld for 28 consecutive days because of treatment-related toxicity, the treatment should be discontinued.** Treatment may be suspended for reasons other than toxicity (e.g., surgical procedures) with investigator approval. If, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming study treatment after a hold of >28 consecutive days, study drug may be restarted. This applies to ipatasertib, carboplatin/paclitaxel or carboplatin.

5.1.5.7 Adverse Event Management Guidelines

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

5.1.5.7.1 Diarrhea Management Guidelines

Specific guidelines for managing diarrhea to improve safety and tolerability are provided in **Table 5.** In this study, 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. Patients 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.

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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 ≥ Grade 3 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.

Dose intensity of paclitaxel should be maintained as tolerated. Dose reductions of ipatasertib will be by one level at a time (i.e., 400 to 300 mg; 300 to 200 mg) as outlined in **Section 5.1.5.1** and **Table 2. .** If Grade ≥2 diarrhea persists following dose reductions of ipatasertib 200 mg daily and with maximum treatment for diarrhea, ipatasertib should be discontinued

Table 5 Diarrhea Management Guidelines

Severity of Diarrhea [a]	Management Guideline
Prevention	• **All patients are mandated to receive loperamide (2 mg BID or 4 mg QD) as prophylaxis for diarrhea in the first cycle.** Loperamide dose adjustment may be made per investigator discretion. • After the first cycle, patients 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.

Grade 2 Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline	• Rule out infectious etiology. • 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.** • Interrupt capecitabine until diarrhea improves to Grade 1 or better. Capecitabine can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce Capecitabine by one dose level for recurrent Grade 2 diarrhea. • When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.

Table 5 Diarrhea Management Guidelines (cont.)

Severity of Diarrhea [a]	Management Guideline
Grade 3 Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • For ≥ Grade 3 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]). • 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.** • Interrupt capecitabine until diarrhea improves to Grade 1 or better. Capecitabine can be resumed at one dose lower per investigator's evaluation upon improvement to Grade 1 or better. • Reduce Capecitabine by one dose level for recurrent Grade 3 diarrhea.When study treatment is resumed, loperamide prophylaxis should also be resumed and continues as clinically indicated, if allowed by local guidance.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Rule out infectious etiology. • Treat per Grade 2 management guidelines and supportive care. • Permanently discontinue ipatasertib and Capecitabine

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 frequent and watery bowel movements.

5.1.5.7.2 Fasting Hyperglycemia

Fasting is defined as abstaining from food and drink (with the exception of water) for at least 8 hours.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (see **Table 6**) 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.

Home glucose measurements may be used to trigger contact between patient and investigative site team and may lead to an unscheduled clinic visit to assess fasting glucose. Guidance for

when to call the investigator/site staff (or designated endocrinologist, if applicable) should be provided to patients for hypoglycemia (e.g., glucose value under 70 mg/dL) and hyperglycemia (e.g., glucose value over 300 mg/dL). Alternative thresholds may be selected as clinically indicated per investigator discretion or institutional guidance and noted in the source documents. For any patients performing home glucose monitoring, the blood glucose log should be reviewed at each clinic visit (and source data retained), entry of results into the patient's eCRF will be limited to values which result in intervention.

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.

Table 6 Fasting Hyperglycemia Management Guidelines

Severity of Fasting Hyperglycemia	Management Guideline
Grade 1: Abnormal glucose above baseline with no medical intervention	• Monitor fasting glucose per protocol • Consider initiating home glucose monitoring
Grade 2: Change in daily management from baseline for a diabetic; oral antihyperglycemic agent initiated; workup for diabetes	• Interruption of ipatasertib until fasting hyperglycemia resolves to Grade 1 or better. • Initiate home glucose monitoring • Start oral anti-diabetic medications (e.g., metformin). • If patient is already on an oral anti-diabetic medication, the dose of ipatasertib should be reduced by one dose level • 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.
Grade 3: Insulin therapy initiated; hospitalization indicated	• Interrupt ipatasertib dosing until fasting hyperglycemia resolves to Grade 1 or better. • Initiate home glucose monitoring • Treat hyperglycemia as medically appropriate. Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • 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 Grade $\geq$ 3 fasting hyperglycemia recurs, the dose of ipatasertib should be reduced by one dose level when treatment is restarted.

Grade 4: Life-threatening consequences; urgent intervention indicated	• Interrupt ipatasertib dosing until resolution to Grade 1 or better. • Treat hyperglycemia as medically appropriate. • Initiate home glucose monitoring • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Reduce ipatasertib by one dose level if and when treatment is restarted. • If Grade 4 hyperglycemia recurs, permanently discontinue ipatasertib

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

5.1.5.7.3 Neutropenia and/or Thrombocytopenia

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 and/or paclitaxel are outlined in **Table 7** .

Table 7 Neutropenia and Thrombocytopenia Management Guidelines

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 2	• Ipatasertib or capecitabine may be continued at the original dose. Carboplatin or Carboplatin/Paclitaxel must be held till ANC has recovered to ≥ 1500/μL and when the platelet count has recovered to ≥ 100,000/μL for day 1 of each cycle. • For days 8 or 15 of each cycle, carboplatin or carboplatin/paclitaxel may be administered up to 14 days (2 doses), even with Grade 2 neutropenia, without a dose reduction, as long as G-CSF is used to manage the neutropenia. • If the hematologic criteria do not recover to Grade 1 or better within the 14-day window of treating for ongoing Grade 2 neutropenia, the subsequent carboplatin or carboplatin/paclitaxel dose(s) must be held until recovery of hematological criteria to Grade 1 or better.

Table 7 Neutropenia and Thrombocytopenia Management Guidelines (cont.)

Severity of Neutropenia and/or Thrombocytopenia	Management Guideline
Grade 3	• Ipatasertib, capecitabine and carboplatin or carboplatin/paclitaxel 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: If recovery is to Grade 1, resume the original dose. 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. If recovery is to Grade 2, follow the guidance above. – Recurrent episode: Ipatasertib, capecitabine and carboplatin or carboplatin/paclitaxel should be reduced by one dose level when treatment is restarted. **If patient has had more than three Grade 3 neutropenia episodes on study, despite the above dose reduction, chemotherapy should be permanently discontinued and patient may continue to receive ipatasertib.** • Following a treatment hold of up to 4 weeks, if recovery to Grade 2 or better neutropenia does not occur, the patient may continue therapy
Febrile neutropenia and Grade 4 neutropenia	• Ipatasertib , capecitabine and carboplatin or carboplatin/paclitaxel 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, capecitabine and carboplatin or carboplatin/paclitaxel should be reduced by one dose level when treatment is restarted. – **Recurrent episode: Ipatasertib,** capecitabine **and carboplatin or carboplatin/paclitaxel 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 therapy.

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

5.1.5.7.4 GI: Nausea / Vomiting and Hepatotoxicity

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 8). For persistent nausea and/or vomiting attributable to ipatasertib, dosage modification guidelines are outlined in **Section 5.1.5.1**, **Table 1** and **Table 8A**). For hepatotoxity attributable to study drug, dosage modification guidelines are outlined in **Table 8B**.

Table 8A 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. • The dose of capecitabine or carboplatin or carboplatin/paclitaxel may be reduced by one level if recurrent grade 3 nausea or vomiting occurs after dose reduction of ipatasertib has occurred.

Table 8B 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 treatment. On return of LFTs to baseline or to AST and ALT ≤ 2.5 × ULN and total bilirubin ≤ 1.5 × ULN levels, restart ipatasertib at previous dose level 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 The dose of capecitabine or carboplatin or carboplatin/paclitaxel may be reduced by one level if recurrent grade 3 LFT occurs after dose reduction of ipatasertib has occurred 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.

5.1.5.7.5 Rash

Ipatasertib should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dosage modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in **Table 9** (see **Section 5.1.5.1**, **Table 1**, and **Table 9** for dose modifications).

Table 9 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. • Follow above guidance and reduce ipatasertib by one dose level for recurrent Grade 2 rash. • For Grade 3 Palmar-plantar Erythrodysesthesia induced by capecitabine, hold dose till grade 1 or better, dose reduce capecitabine by 1 dose level
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. • For Grade 3 Palmar-pantar Erythrodysesthesia induced by capecitabine, hold dose till grade 1 or better, dose reduce capecitabine by 1 dose level
Grade 4	• Administration of systemic steroids (oral or intravenous) is recommended. Consider dermatological consultation and skin biopsy. Ipatasertib should be permanently discontinued.

5.1.5.7.6 Pneumonitis

Pneumonitis is not known to be causally related to any of the study drugs; 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 10**).

Table 10 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 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.

5.1.5.7.7 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 11**.

Table 11 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. The dose of capecitabine, carboplatin or carboplatin/paclitaxel may be maintained for subsequent cycle.
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. The dose of capecitabine, carboplatin or carboplatin/paclitaxel may be reduced for subsequent cycle per investigator's discretion. • If recovery of mucositis to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue ipatasertib.

5.1.5.7.8 Peripheral Neuropathy

If Grade ≥3 peripheral neuropathy attributable to paclitaxel develops in patients, paclitaxel should be held until the neuropathy recovers to Grade 2 or better, or resolution such that the peripheral neuropathy is no longer clinically significant. During this time,
patients may continue ipatasertib/carboplatin.

If the peripheral neuropathy recovers to Grade 2 or better within 4 weeks or resolution such that the peripheral neuropathy is no longer clinically significant, dosing of paclitaxel may resume reduced by one dose level (see **Section 5.1.5.3**).

If recovery of the peripheral neuropathy to Grade 2 or better does not occur within a maximum of 4 weeks, the patient will permanently discontinue paclitaxel but may continue the ipatasertib/carboplatin.

5.1.5.7.9 Hypersensitivity Reactions

If a hypersensitivity reaction due to infusion of paclitaxel or carboplatin develops in patients, treatment for the hypersensitivity reaction, including the possibility of rechallenging with the attributable chemotherapy agent, in presence of premedication for paclitaxel or carboplatin should be administered as per institutional guidelines or at the discretion of the investigator.

Caution: Patients who had a mild to moderate hypersensitivity reaction have been successfully rechallenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

If patients develop severe allergy to paclitaxel despite adequate premedication, weekly nab-paclitaxel can be used to replace weekly paclitaxel following standard institutional practice after discussion with PI.

Subjects who have developed hypersensitivity reactions may undergo desensitization per institutional protocol. This should be discussed with the study PI. The patient may continue the other study treatment components not associated with the toxicity (i.e., ipatasertib or carboplatin or paclitaxel)

Mild symptoms: *(e.g., mild flushing, rash, pruritus) - Complete infusion. Supervise at bedside. No treatment required.*

Moderate symptoms: *(e.g., moderate rash, flushing, mild dyspnea, chest discomfort) - Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate, 20 mg/hr. For 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop infusion. Record toxicity on flow sheets.*

Severe life threatening symptoms: (e.g., hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria) - Stop infusion. Give intravenous diphenhydramine and dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to bronchodilators, epinephrine is recommended. Patient should be removed from further protocol therapy. Report as an adverse event.

5.1.5.7.10 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. During this time, treatment may continue with the other non-attributable treatment agent (i.e., either ipatasertib or carboplatin or carboplatin/paclitaxel). Grade ≥3 non-hematologic toxicity should be monitored at least weekly.

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 2–4 weeks, the dose of the attributable drug should be reduced by one level per the suggested guidelines in **Section 5.1.5.1**.

Depending on the nature and the severity of the adverse event, if recovery to Grade 1 or better takes >4 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.

5.1.5.7.11 Specific Management Guidelines for Arm 3 Atezolizumab Toxicities

Toxicities associated or possibly associated with atezolizumab/placebo treatment should be managed according to standard medical practice. Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.

If atezolizumab must be held for > 12 weeks for toxicities related to atezolizumab, atezolizumab must be discontinued.

5.1.5.7.11.1 Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients should be assessed for pulmonary signs and symptoms throughout the study.

All pulmonary events should be thoroughly evaluated for other potential etiologies such as pneumonia or other infection, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in **Table 5.1.5.7.11A.**

Table 5.1.5.7.11A. Management guidelines for pulmonary events, including pneumonitis, related to atezolizumab

Event	Management
Pulmonary event, Grade 1	• Continue atezolizumab and monitor closely. • Consider diagnostic imaging. • Consider patient referral to pulmonary specialist.
Pulmonary event, possibly related to atezolizumab, Grade 2	• Hold atezolizumab. • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage. • If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Pulmonary event, Grade 3 or 4	• Refer patient to pulmonary and infectious disease specialists for bronchoscopy or bronchoscopic alveolar lavage. • Discontinue atezolizumab and initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.2 Hepatic Events

Immune-related hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in **Table 5.1.5.7.11B**.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 5.1.5.7.11B. Management guidelines for hepatic events related to atezolizumab

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab and monitor closely. If LFT values are above normal limits, monitor LFTs weekly.
Hepatic event, Grade 2	• Hold atezolizumab and recheck LFTs in 3-7 days. - If LFTs are improving or have increased by < 25 IU and remain Grade 2, monitor LFTs weekly until LFTs return to ≤ Grade 1. - If LFTs increase further by a minimum of 25 IU but remain Grade 2, discontinue atezolizumab, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hepatic event, Grade 3 or 4	• Refer to hepatic specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Discontinue atezolizumab and initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.3 Gastrointestinal Events

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table xx

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five

specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm immune colitis diagnosis.

Table 5.1.5.7.11C Management guidelines for gastrointestinal events (diarrhea or colitis) related to atezolizumab

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for > 7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Hold atezolizumab • Initiate symptomatic treatment. • Refer to GI specialist for evaluation and sigmoidoscopy. • If immune colitis documented or if events persist > 5 days, discontinue atezolizumab and initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. • When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Diarrhea or colitis, Grade 3 or 4	• Refer patient to gastrointestinal specialist for evaluation and sigmoidoscopy with possible biopsy. • Discontinue atezolizumab and initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.4 Endocrine Events

Thyroid disorders or adrenal insufficiency has been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in **Table 5.1.5.7.11D**. Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Table 5.1.5.7.11D. Management guidelines for endocrine events related to atezolizumab

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone.
Symptomatic hypothyroidism	• Hold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Hold atezolizumab and refer to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • For life-threatening hyperthyroidism discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Symptomatic adrenal insufficiency, Grade 2-4	Refer patient to endocrinologist. • Discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Hyperglycemia, Grade 1, 2, or 3	• Continue atezolizumab. • Initiate treatment with insulin if needed. • Monitor for glucose control.
Hyperglycemia, Grade 4	• Initiate treatment with insulin. • Discontinue atezolizuma and initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).
Management guidelines for ocular events are provided in Table **Table 5.1.5.7.11E**.

5.1.5.7.11E. Management guidelines for ocular events related to atezolizumab

Event	Management
Ocular event, Grade 1	• Continue atezolizumab • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, manage as a Grade 2 event.
Ocular event, Grade 2	• Hold atezolizumab • Refer to ophthalmologist. • If immune-related toxicity is suspected, permanently discontinue atezolizumab, initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy.
Ocular event, Grade 3 or 4	• Refer patient to ophthalmologist. • Permanently discontinue atezolizumab, initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.6 Infusion-related reactions

No premedication is indicated for the administration of Cycle 1 of atezolizumab.
However, patients who experience an infusion-related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.
Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in **Table 5.1.5.7.11F**. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 5.1.5.7.11F Management guidelines for infusion-related reactions related to atezolizumab/placebo

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, monitor for an additional 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	

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	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for infusion-related reactions.
IRR, Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab

5.1.5.7.11.7 Management of pancreatic events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate work-up should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table **5.1.5.7.11G**.

Table 5.1.5.7.11G. Management guidelines for pancreatic events, including pancreatitis, related to atezolizumab

Event	Management
Asymptomatic amylase and/or lipase elevation, Grade 1	• Continue atezolizumab. • Monitor amylase and lipase prior to dosing.
Asymptomatic amylase and/or lipase elevation, Grade 2	• Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), hold atezolizumab. • Refer patient to gastrointestinal specialist. • If non-immune etiology not identified, discontinue atezolizumab and begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Amylase and/or lipase elevation, Grade 3 or 4	• Refer patient to gastrointestinal specialist. • Discontinue atezolizumab and begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Immune-related pancreatitis, Grade 2, 3, or 4	• Refer patient to gastrointestinal specialist. • Discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement.

	- If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.8 Management of Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 5.1.5.7.11H.

Table 5.1.5.7.11H Management for dermatologic events related to atezolizumab

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Refer to dermatologist and consider skin biopsy. • Initiate treatment with topical corticosteroids. • If rash does not improve, discontinue atezolizumab, initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Dermatologic event, Grade 3 or 4	• Refer patient to dermatologist. • Discontinue atezolizumab, initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.8 Management of Neurological Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 5.1.5.7.11I.

Table 5.1.5.7.11I Treatment management guidelines for neurological disorders related to atezolizumab/placebo

Event	Management
Neuropathy, Grade 1	Continue atezolizumab
Sensory neuropathy, Grade 2	• Refer patient to neurologist. • Discontinue atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Motor neuropathy Grade 2	• Refer patient to neurologist. • Discontinue atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Neuropathy, Grade 3 or 4	• Refer patient to neurologist. • Discontinue atezolizumab, begin treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Refer patient to neurologist and initiate treatment as per institutional guidelines. • Discontinue atezolizumab, begin treatment with 1-2 mg/kg/day oral or intravenous prednisone or equivalent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.9 Management of meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.
All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table **5.1.5.7.11.J**.

Table 5.1.5.7.11.J. Management guidelines for immune-related meningoencephalitis related to atezolizumab

Event	Management
Immune-related meningoencephalitis, all grades	• Refer patient to neurologist. • Permanently discontinue atezolizumab, initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.10 Management and Evaluation of Elevated Creatinine (Potential Immune-Related Nephritis)

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function defined as baseline calculated creatinine clearance ⩾ 50 mL/min, and renal function will be monitored throughout study treatment. Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 5.1.5.7.11.K.

For patients with elevated creatinine, concurrent medication, volume depletion, renal obstruction should be considered and addressed, as appropriate. Refer to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Table 5.1.5.7.11.K. Management and evaluation of elevated creatinine (potential immune-related nephritis)Event	Management
Creatinine elevation, Grade 1 (> ULN to 1.5 x ULN)	• Continue/resume atezolizumab. • If creatinine value is above normal limits, monitor weekly.
Creatinine elevation, Grade 2 (>1.5 to 3.0 x ULN)	• Hold atezolizumab and recheck creatinine in 3-7 days. - If creatinine is improving but remains Grade 2, continue to hold atezolizumab and monitoring creatinine weekly until ≤ Grade 1. - If repeat creatinine value does not improve but remains Grade 2, refer to nephrologist for evaluation and continue to hold atezolizumab. - If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab and initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent.

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	When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Creatinine elevation, Grade 3 (> 3.0 to 6.0 x ULN) **OR** Grade 4 (> 6.0 x ULN)	• Refer to nephrologist for evaluation and consideration of renal biopsy to establish etiology of renal injury. • Discontinue atezolizumab, initiate treatment with 1−2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.11 Management of Immune-related myositis

Immune-related myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are amongst the most common disorders. The diagnosis is based on clinical signs and symptoms (muscle weakness, muscle pain, skin rash in dermatomyositis) supported by confirmatory diagnostic studies such as biochemical markers (serum creatine-kinase increase), electromyography, and imaging (MRI) features, which may be confirmed with a muscle-biopsy. Patients presenting with muscle pain without muscle weakness should have atezolizumab held pending evaluation for possible myositis. Referral to a neurologist should be considered for patients presenting with weakness. Patients with symptoms and confirmation of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 5.1.5.7.11L.

Table 5.1.5.7.11L. Management and evaluation of immune-related myositis

Event	Management
Myositis, Grade 1 (mild pain with elevated CK)	• Hold atezolizumab. • Refer patient to rheumatologist or neurologist. • If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - When CK elevation resolves and pain improved, taper corticosteroids over ≥ 1 month. • If non-immune etiology identified, may resume or discontinue atezolizumab per investigator discretion.
Myositis, Grade 2 (moderate pain with weakness)	• Hold atezolizumab. • Refer patient to rheumatologist or neurologist. • If evaluation fails to define non-immune etiology OR defines an immune etiology, discontinue atezolizumab

	and initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month. • If non-immune etiology identified, may resume or discontinue atezolizumab per investigator discretion
Myositis, Grade 3 (pain with severe weakness)	• Hold atezolizumab. • Refer patient to neurologist or rheumatologist. • Evaluate for associated myocarditis and consider consulting cardiologist. • Respiratory support may be required in more severe cases. • Discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day IV methylprednisolone or equivalent or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility) and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

5.1.5.7.11.12 Management of Immune-related cardiac toxicity

Cardiac toxicity is a potential toxicity with the use of atezolizumab. Patients should be monitored for signs and symptoms of left ventricular dysfunction and cardiac arrhythmias. Consider echocardiogram and ECG. For Grade 2 symptomatic cardiac toxicities refer to cardiologist for a cardiac evaluation. Consider endomyocardial biopsy and initiation of oral steroids. For Grade 3 or Grade 4 cardiac toxicities, hospitalize, obtain a cardiology consult and obtain endomyocardial biopsy unless contraindicated. Treat with intravenous steroids followed by high dose oral steroids. See Table 5.1.5.7.11M for management of symptomatic cardiac toxicities related to atezolizumab.

Table 5.1.5.7.11M. Treatment modifications and instructions for **symptomatic** cardiac toxicities related to atezolizumab

Event	Management
Myocarditis or Heart Failure Grade 1,2	• Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and ECG. • Consider endomyocardial biopsy. • Discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • When event resolves to Grade 1 or better, taper

	corticosteroids over ≥ 1 month.
Myocarditis or Heart Failure Grade 3,4	• Admit to the hospital. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and ECG. • Endomyocardial biopsy should be considered unless medical condition precludes the biopsy. • Discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
Left Ventricular Dysfunction Grade 3,4	• Admit to the hospital. • Consult cardiologist to conduct cardiac evaluation including LVEF assessment, troponin, and ECG. • Endomyocardial biopsy should be considered unless medical condition precludes the biopsy. • Discontinue atezolizumab and initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. - If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. - When event resolves to Grade 1 or better,

6. GENENTECH ADVERSE EVENT REPORTING, DATA & SAFETY MONITORING PLAN

ASSESSMENT OF SAFETY

Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified
- AE reporting period, including signs or symptoms associated with metastatic breast cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated

with medication washout, no treatment run-in, or other protocol-mandated intervention.

- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Serious Adverse Events

An AE should be classified as an SAE if the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR.

Adverse Event Reporting Period

The study period during which AEs and SAEs as described in ***section J*** where the patient has been exposed to Genentech product must be reported Reporting period begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment (Modify statement depending up on section **g**).

Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see

following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of the study drug, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug; and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the {study drug} (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in current Investigator Brochure.

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last

here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section I), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical

procedures for preexisting conditions

- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

e. Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0 Update current versions) will be used for assessing adverse event severity. Below Table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 12. Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

f. Pregnancy

If a female subject or the female partner of a male study subject becomes pregnant while receiving the study drug or within 5 months after the last dose of study drug, a report should be completed and expeditiously submitted to Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any

congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

g. Post-Study Adverse Events

For studies involving collection of survival data/ follow up until progression free period/ Extended follow up period (select applicable) the investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drug) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study that is believed to be related to prior exposure to study drug.
Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports.

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior study drug exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject [add if applicable-including pregnancy occurring in the partner of a male study subject] who participated in the study, this should be reported as an SAE adequately to Genentech drug Safety during follow up period.

h. Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via City of Hope emailing Genentech a Quarterly line-listing documenting single case reports sent by City of Hope to Genentech in the preceding time period.

The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Sponsor and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The sponsor shall receive reconciliation guidance documents within the ‘Activation Package’.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by City of Hope to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech

i. AEs of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the

.

Sponsor is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

Adverse events of special interest for this study 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:
    - Treatment-emergent ALT or AST > 3 folds changes from baseline in combination with total bilirubin > 2 folds changes from baseline
    - Treatment-emergent ALT or AST > 3 folds changes from baseline in combination with clinical jaundice

The Ipatasertib Events of Special Interest Are:

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    - Grade ≥ 3 hepatotoxicity
    - Grade ≥ 3 fasting hyperglycemia
    - Grade ≥ 3 ALT/AST elevations
    - Grade ≥ 2 colitis/enterocolitis
    - Grade ≥ 3 diarrhea
    - Grade ≥ 3 rash
    - Grade ≥ 2 pneumonitis

Additional data will be collected for the following adverse events:

- Diarrhea
- Asthenia (fatigue)
- Nausea
- Peripheral neuropathy (peripheral sensory neuropathy, neuropathy peripheral, peripheral motor neuropathy)
- Neutropenia (neutrophil count decreased, febrile neutropenia)
- Rash (e.g., maculopapular, erythema, urticarial, dermatitis, rash popular, skin exfoliation, toxic skin eruption)
- Erythema multiforme
- Vomiting
- Oral mucositis (stomatitis, mucosal inflammation, mouth inflammation, mouth ulceration)

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- Hyperlipidemia (hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, blood cholesterol increased, blood triglycerides increased)
- Hepatotoxicity (ALT, AST increased)
- Hyperglycemia (blood glucose increased)
- Pneumonia (lower respiratory tract infection)
- Pneumonitis (interstitial lung diseases)

The Atezolizumab Adverse Events of Special Interest Are:

Adverse events of special interest for this study are as follows:

- 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 (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study treatment, 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 study treatment is suspected.

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10xULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness and systemic inflammatory response syndrome.
- Nephritis Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

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- Pneumonitis ⩾ Grade 2

j. Exchange OF SINGLE CASE REPORTS

City of Hope will track all protocol-defined AE and pregnancy reports originating from the stdudy. Investigators must report all Adverse Events/ Serious Adverse events (SAEs), AEs of Special Interest (AESIs) pregnancy reports, product complaints (with or without AE), and special situation reports (if applicable) adequately to Genentech within the timelines described below.

Investigators must report all the above mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form (**Appendix 3**) or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints with an AE should be sent to:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints without an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Relevant follow-up information should be submitted to Genentech Drug Safety as soon as it becomes available and/or upon request

All SAEs, AESIs, pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE) where the patient has been exposed to the Genentech Product, shall be transmitted to Genentech on a MedWatch or CIOMS I or on Genentech approved SAE form within one (1) business day of the awareness date.

City of Hope will forward quarterly listings of non-serious AEs (Including Special Situation reports) originating from the Study to Genentech/Roche

Special situation reports

In addition to all SAEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Drug interaction

In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported

Product Complaint

All Product Complaints (with or without an AE) shall be forwarded to Genentech within one (1) business day of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form summarizing new information and faxing it with a cover letter

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including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at
http://www.fda.gov/downloads/AboutFDA/ReportsManualsFo rms/Forms/UCM048334.pdf

REPORTING TO REGULATORY AUTHORITIES, ETHICS COMMITTEES AND INVESTIGATORS

City of hope will be responsible for the distribution of safety information to its own investigators, where relevant

Additional Reporting Requirements for IND Holders (if applicable):

For Investigator-Initiated IND Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of study drugs. An unexpected adverse event is one that is not already described in the study drugs Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech/Roche within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of study drugs. An unexpected adverse event is one that is not already described in the study drugs investigator brochure.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech/Roche, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for IND Safety Reports:

Fax: 1 (800) FDA 0178

All written IND Safety Reports submitted to the FDA by the Investigator must also be faxed to
Genentech/Roche Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

AGGREGATE REPORTS

IND ANNUAL REPORTS

All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech

Copies of such reports should be emailed to Genentech at: Genentech Drug Safety CTV mail box: ctvist_drugsafety@gene.com

Other Reports

City of Hope will forward a copy of the Final Study Report to Genentech/Roche upon completion of the Study.

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

And to Genentech Drug Safety CTV oversight mail box at: ctvist_drugsafety@gene.com

QUERIES

Queries related to the Study will be answered by City of Hope. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche shall have the final say and control over safety queries relating to the Product. City Of Hope agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

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SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche shall have the final say and control over safety crisis management issues relating to the Product. City of Hope agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche.

7. COH DATA AND SAFETY MONITORING

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern. This is a Risk Level 4 study as defined in the **City of Hope Institutional Data and Safety Monitoring Plan.** This determination was made because the study involves a COH IND.

Definition of Risk level

Adverse Event (AE)

An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Serious Adverse Event (SAE)

A serious adverse event is any expected or unexpected adverse events that result in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary malignancy*
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

*Modified from 21 CFR 312.32

Unanticipated Problems Involving Risks to Subjects or Others

An unanticipated problem is any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Adverse Events of Special Interest (AESI)

See section 6

Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, assessing the severity (i.e. grade), expectedness, and attribution of all adverse events.

Assessment of Adverse Event Name and Grade

Adverse events will be characterized using the descriptions and grading scales found in the most recent version of CTCAE 5.0. The determination of severity for all other events not listed in CTCAE 5.0 the should be made by the investigator based on medical judgment and the severity categories of Grade 1 to 5 as defined below:

- Grade 1 (mild) – An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate) – An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe) – An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening) – An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal) – Death (loss of life) as a result of an event.

Assessment of Attribution

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.

- **Unlikely –** The event is doubtfully related to the investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions, or concomitant drugs.
- **Definite –** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs, AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

Assessment of Expectedness

The following definitions will be used to determine the expectedness of the event:

- **Unexpected** – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event. *Modified from 21 CFR 312.32 (a)
- **Expected –** An adverse event is expected if it does not meet the criteria for an unexpected event, OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

REPORTING OF ADVERSE EVENTS

Routine Reporting of Non-Serious Adverse Events

Routine AE recording will occur via data entry into the study eCRF. Recording of adverse events will begin once the patient is consented and will continue until 30 days post study. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

EXPEDITING REPORTING REQUIREMENTS OF SAES AND UPS

Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope's Institutional policy via the AE/UP reporting form in iRIS. Reportable serious adverse events must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

Additional AE Reporting Requirements

Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope's Institutional policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the Medwatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

In addition, the study PI will submit annually within 60 days (via COH OIDRA) of the anniversary date of when the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

Reporting to Genentech

All serious adverse events and AESIs (initial and follow-up information) will be reported by the study PI to Genentech per **Section 6**.

1. The following events will be reported using a MedWatch form in an expedited manner to Roche/Genentech Global Safety **within 24 hours** of being aware of the event (via OIDRA) (**Table 13**).
2. SAE reports and any other relevant safety information will be forwarded to the Roche/Genentech Global Safety facsimile number 215 993-1220 (Attn: Worldwide Product Safety).
3. Copies of all FDA reports cross-referencing the IND will also be submitted to Roche/Genentech (Attn: Worldwide Product Safety; FAX 215 993-1220) at time of FDA submission (via OIDRA).
4. Report to Roche/Genentech aggregate safety information every 3 months at time of COH PMT report.
5. Participating sites will report these events directly to the COH PI and the DCC who in turn will report to Roche/Genentech

Table 13. Expedited Reporting to Roche/Genentech

Timepoint	What to report to Roche/Genentech
Screening up to Day 1 of protocol therapy	• Pregnancy and lactation • Any reason for not starting Day 1 of protocol therapy
For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier **All reportable events will require follow up until stabilization or resolution per the agreement of the Study PI.**	• All SAEs regardless of relationship to protocol therapy, study procedure, underlying disease or concomitant treatment. • Death due to any cause other than progression of the cancer under study • All AEs that meet the definition of a UP • Overdose of either agent • Pregnancies and lactation • Abnormal liver function tests
For participants yet to initiate anti-cancer therapy: From Day 1 of therapy up to 120 days post-last pembrolizumab dose	• Pregnancies and lactation
Post Safety follow-up to removal from study	• All SAEs that are considered possibly, probably, or definitely related to pembrolizumab.

PROTOCOL DEVIATIONS AND SINGLE SUBJECT EXCEPTIONS

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Brief interruptions and delays may occasionally be required because of travel delays, airport closures, inclement weather, family responsibilities, security alerts, government holidays, and so forth. Delays can also extend to complications of disease or unrelated medical illnesses not related to disease progression. The PI has the discretion to deviate from the protocol when necessary so long as such a deviation does not threaten patient safety or protocol scientific integrity. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

Definitions

Deviation

A deviation is a divergence from a specific element of a protocol that occurred without prior IRB approval. Investigators may deviate from the protocol to eliminate immediate hazard(s) for the protection, safety, and well-being of the study subjects without prior IRB approval. Examples include, but are not limited to: a) dose adjustments based on excessive patient weight; b) alteration in treatment schedule due to non-availability of the research participant for treatment; and c) laboratory test results which are slightly outside the protocol requirements but at levels that do not affect participant safety.

Single Subject Exceptions (SSE)

An SSE is a planned deviation, meaning that it involves circumstances in which the specific procedures called for in a protocol are not in the best interests of a specific patient. It is a

deviation that is anticipated and receives **prior** approval by the Principal Investigator and the COH IRB.

Reporting of Deviations and SSEs

Reporting Deviations

For any deviation, the Investigator will notify the COH DSMC and IRB within 5 calendar days of its occurrence via iRIS in accordance with the Clinical Research Protocol Deviation policy and Genentech requirement (**Refer to Section 6**)

Reporting Single Subject Exceptions

The SSE must be submitted as a "Single Subject Exception Amendment Request" via iRIS in accordance with IRB guidelines and the Clinical Research Protocol Deviation policy. An IRB approved SSE does not need to be submitted as a deviation to the DSMC.

In addition, if contractually obligated, the sponsor must also approve the deviation.

STUDY OVERSIGHT, QUALITY ASSURANCE, AND DATA & SAFETY MONITORING

ALL INVESTIGATOR RESPONSIBILITIES

AN INVESTIGATOR IS RESPONSIBLE FOR ENSURING THAT AN INVESTIGATION IS CONDUCTED ACCORDING TO THE SIGNED INVESTIGATOR STATEMENT, THE INVESTIGATIONAL PLAN, AND APPLICABLE REGULATIONS; FOR PROTECTING THE RIGHTS, SAFETY, AND WELFARE OF SUBJECTS UNDER THE INVESTIGATOR'S CARE; AND FOR THE CONTROL OF DRUGS UNDER INVESTIGATION.

All Investigators agree to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

STUDY PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312. Subpart D are executed in accordance with federal regulations.

PROTOCOL MANAGEMENT TEAM (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) at least monthly to review study status. This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The meeting will be a forum to discuss study related issues including accrual, SAE/AEs experienced, study response, deviations/violations and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed. It is recommended that minutes of these discussions be taken to document the date of these meetings, attendees and the issues that were discussed (in a general format).

MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

The Investigator will permit the study monitors and appropriate regulatory authorities direct access to the study data and to the corresponding source data and documents to verify the accuracy of this data. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

Details of clinical site monitoring are documented in the OCTAM SOP. This document specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of subject data to be reviewed), and the distribution of monitoring reports. Staff from OCTAM will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SOP. Documentation of monitoring activities and findings will be provided to the study team, and the COH DSMC.

QUALITY ASSURANCE

The City of Hope Clinical Research Information Support will provide support for this multi-center trial as detailed in the COH DCC Operations Plan provided as a supplement to this document.

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CITY OF HOPE DATA AND SAFETY MONITORING COMMITTEE

This is a risk level 4 study as defined in the City of Hope Institutional Data and Safety Monitoring Plan. This determination was made because the study involves phase I study and COH held IND.

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The Study Principal Investigator is required to submit periodic status reports (the PMT report) according to the guidelines outlined in the City of Hope Institutional Data and Safety Monitoring Plan. The PMT report will be submitted to the COH DSMC quarterly from the date of activation.

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The DSMC will review up-to-date participant accrual; summary of all adverse events captured via routine and expedited reporting; a summary of deviations; any response information; monitoring reports, and summary comments provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. For Phase I studies, a Phase I Tracking Log will be utilized and reviewed by the DSMC to monitor data and safety for dose escalation. A review of outcome results (response, toxicity and adverse events) and factors external to the study (such as scientific or therapeutic developments) is discussed, and the Committee votes on the status of each study. Information that raises any questions about participant safety will be addressed with the Principal Investigator, statistician and study team.

8. CORRELATIVE STUDIES

8.1 TUMOR TISSUE STUDIES

An overview of collection, processing, and analysis details are shown in **Table 14**.

Table 14 Tumor tissue studies overview

Tissue Type	Timepoint of collection	Materials per Timepoint	Material Submitted	Type of Laboratory Analysis
Formalin fixed (FFPE) tissue from core needle or surgical specimen or other procedure	• Baseline • Cycle 2 Day 1	20- 30 unstained slides	5 um cut blank slides	Nanostring Expression analysis

Tissue Type	Timepoint of collection	Materials per Timepoint	Material Submitted	Type of Laboratory Analysis
	• End of protocol therapy			

- Baseline tissue:
  - FFPE (up to 42 days old from Day 1 of protocol therapy): A sample should be submitted within 14 days post-registration. If a recently-obtained sample is unavailable an archived metastatic specimen not previously irradiated may be submitted upon agreement from the Study PI.
  - Fresh tissue (after consent): If a standard of care procedure is to be performed, attempts should be made to take extra tissue for research.
- Cycle 2 Day 1: Submit fixed and if available, fresh tissue for research if the participant is willing.
- End of protocol therapy: FFPE and if also available fresh tissue obtained for standard of care purposes to be submitted within 1 month of discontinuing therapy.

8.1.1 Labeling

Label samples with COH protocol #, subject ID and timepoint of collection (e.g. baseline or EOT). A sample manifest will be maintained by the PI or designee.

8.1.2 Distribution to laboratories for analysis

Fresh tissue samples in PBS or RPMI media should be submitted to Karen Miller or designee at the COH Biorepository Core immediately on ice within 2 hours of collection. If possible, at **least 1 day advance notice** should be given to Karen Miller or designee.

If applicable, the COH Biorepository Core will distribute fixed tissue/ diagnostic tissue to internal and external laboratories for analysis (see **Table 14**).

8.2 OVERVIEW OF PERIPHERAL BLOOD STUDIES

Blood samples will be collected from an indwelling venous catheter or by venipuncture for the below stated analyses (see **Table 15**). **Arm C** peripheral blood will be obtained on C1D1, C2D1, C4D1 and EOT to track the temporal dynamics of the host immune response.

Table 15 Peripheral blood studies overview

Timepoint of collection	Volume	Tube Type	Processing/ Receiving Laboratory
• C1D1 • C2D1 • C4D1 • EOT	10 mL	Heparin green-top	Analytical Pharmacology Core Facility (APCF) at COH
	10 mL	Streck Tube	
	10 mL	Lavender-top	

8.3 PERIPHERAL BLOOD CORRELATIVES

8.3.1 COH APCF Notification, Blood Collection and Labeling

NOTE: It is **highly recommended** that non-Duarte sites arrange for a courier **prior to the participant's clinic visit** given the tight turnaround time for sample delivery to the COH APCF and COH Biorepository (Duarte Campus). For non COH sites, please notify the local blood sample processing laboratory for sample delivery.

Table 16 Peripheral blood collection procedure

Notification to COH APCF of Pending Collection	Tube Type	Labeling and Collection Details	Post-collection Instructions
• Notify **at least one** day in advance) • **Send calendar invite via e-mail**: Leslie Smith-Powell (Lsmith-Powell@coh.org) or Dauhlian Chi (dchi@coh.org)	Green-top Streck tube	1. Label tubes with COH protocol # (For non-COH sites, local protocol #), subject ID, actual collection time in 24-hour format, institution (for CP sites), and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Timepoints of collection are stated in **Appendix 1**. 3. Blood samples will be collected from an indwelling venous catheter or by venipuncture 4. Invert tubes eight times after collection. 5. **Green-top tube: Immediately** place the tubes **on ice**. 6. **Streck tube: room temperature**.	• **Efforts should be made to promptly** deliver the blood samples to the COH APCF, Shapiro room 1042 (Duarte Campus) for processing **within 1-2 hours (± 30 minutes).** - **If delivery of samples fall outside of the above specified window, (1)** a note should be made to the study regulatory binder and other applicable documents (and a reason provided) **AND (2)** the reason should also be communicated to the Study PI/ designee. • **Deliver green top tubes on ice or 4ºC.** • Deliver **Streck tube** at **room temperature**. • **For COH Community Practice sites and non-COH sites, courier deliveries**

Notification to COH APCF of Pending Collection	Tube Type	Labeling and Collection Details	Post-collection Instructions
			should be made to the below address: Dr. Tim Synold Analytical Pharmacology Core Facility Shapiro 1042 City of Hope National Medical Center 1500 E. Duarte Road Duarte, CA 91010
	Lavender-top	1. Label tubes with COH protocol # (For non-COH sites, local protocol #), subject ID, actual collection time in 24-hour format, institution (for CP sites), and timepoint of collection (e.g. D1C1 for Day1 of Cycle 1), and if applicable patient initials. 2. Time points of collection are stated in **Appendix 1** 3. Blood samples will be collected from an indwelling venous catheter or by venipuncture 4. Invert tubes eight times after collection. 5. **Lavender-top tube: Immediately** place the tubes **on ice**.	• **Efforts should be made to promptly** deliver the blood samples to the COH Biorepository Core (Duarte Campus,) for processing **within 1-2 hours (± 30 minutes).** • **Deliver lavender top tubes on ice or 4ºC.** • **For COH Community Practice sites and non-COH sites, courier deliveries** should be made to Dr. Tim Synold Lab (COH APCF)

8.3.2 Processing of samples

Keep blood samples on a rocker set at low speed to mimic circulation and avoid clot formation until processing. Efforts should be made to process the samples **within 4 hours** of collection.

Table 17 Peripheral blood sample processing

Tube Type and Volume	Processing Details	
Green-top (10 mL)	Plasma	1. For plasma preparation **use 10 mL whole blood** from green-top tubes. 2. Centrifuge for 10 minutes at 1800 x g at 4 ºC. 3. The resulting upper plasma layer from each tube will be drawn up sequentially into a sterile 5 mL syringe and pushed through a sterile 0.2/0.8 micron disposable filter. a. **Save** the plasma-depleted portion **for isolation of PBMC (see below)**. 4. The filtered plasma will then be transferred in 500 µL aliquots into multiple appropriately-labeled Starstedt microfuge tubes. 5. To **one aliquot**, add 0.5 mL glycerol/0.02% sodium azide solution to dilute the plasma 50/50 v/v. Keep the diluted plasma sample at -20˚C and do not freeze. 6. All the remaining plasma aliquots will be stored frozen at -80˚C until use.
	Peripheral blood mononuclear cells (PBMC)	7. Any blood remaining in the two green-top tubes used to prepare plasma above will be diluted 1:1 with Hank's Balanced Salt Solution (or equivalent) and combined with the whole blood from the unused green-top tube in a sterile 50 ml conical centrifuge tube. 8. PBMC will then be isolated by Ficoll-gradient per **COH APCF procedures**. 9. Isolated PBMC will be stored in 3 aliquoted tubes and stored at -80˚C until use.
Streck Tube (10 mL)	CtDNA	Follow manufacturer's instruction
Lavender-top (10 mL)	Plasma and Plasma depleted whole blood cells (PDWB)	1. Centrifuge for 10 minutes at 820 x g at room temperature. 2. Remove the tubes from the centrifuge. Do not disturb the cellular layer. 3. Extract plasma carefully. **Do not disturb** the **buffy coat** while pipetting plasma; leave ~3-4mm of plasma behind to ensure the buffy coat is undisturbed. 4. Freeze plasma at -80°C in 1-2 mL aliquots. Do not fill tubes beyond 70% capacity.
		5. Mix the remaining PDWB. 6. Freeze PDWB at -80°C in 1-2 mL aliquots.

8.3.3 Sample maintenance and distribution/shipping to laboratories

A sample manifest will be maintained by the PI or designee. Samples will be maintained at APCF until distribution to internal collaborators/external vendors. Samples will be batch shipped to non-COH vendors.

Procedure for plasma/ buffy coat isolation from EDTA tubes: Collect blood in tube until filled. Mix tube by inverting 3-5 times and transport to lab for processing. Samples must be processed within one hour of collection to minimize the possibility of white blood cell lysis. For processing, centrifuge the samples at 820g for 10 min at room temperature and transfer 1 mL aliquots of the plasma to sterile 2 mL microtubes. Freeze plasma aliquots at -80 °C. Remove the Buffy coat layer into a separate pre-labeled tube and store at -80^{0}C. Record corresponding information such as collection time, freezing time, and aliquot number.

Flow Cytometry and single cell RNA sequencing: Peripheral blood mononuclear cells (PBMCs) will be isolated from the blood of patients per manufacturer protocol. For flow cytometry, cells will be stained for immune subtype markers and sorted by fluorescence-activated cell sorting (FACS) or CyTOF. For single cell sequencing, the cells will be loaded in Smarter ICELL8 single cell mRNA chip or the 10x, imaged via microscopy, and single cell libraries will be prepared per manufactures instructions. Next generation sequencing will be performed.

8.4 STOOL SPECIMEN COLLECTION

Fecal samples are relatively easy to collect and non-invasive. They provide an indication of the gut microbiome which may be an indicator of general health, impact drug availability, and indicate the presence of communities associated with inflammation, digestive inefficiencies, and pathogens. Monitoring the gut microbiome may allow us to predict the risk of possible side effects of ipatasertib and therapeutic efficacy.

The exploratory objective to monitor the gut microbiota at baseline, on treatment and end of treatment using fecal samples. The differences in gut microbiota within and between fecal samples will be compared using alpha and beta diversity metrics based on 16S rRNA sequencing.

Stool sample will be collected in a Zymo® Research DNA/RNA Shield Fecal Collection Tube by patients as instructed. A standard operating procedure (SOP) has been generated for stool collection, as outlined in **Appendix 7**.

Stool samples will be collected within 7 days prior to Cycle 1 Day 1, Cycle 4 Day 1 (+/- 7 days), and end of treatment (+/- 7 days).

DIET and Bowel Movement Frequency Log

A copy of this SOP will be provided to the patient and their understanding of the SOP will be documented by the study team (see **Appendix 8**).

Samples will be collected **pre-treatment** (within 7 days of C1D1), **C4 Day 1** (+/-7 days) and end of treatment **EOT visit** (+/-7 days) as described in study calendar. Patient will bring samples on the scheduled study visits.

All samples will be collected by participants at home or during study visit. Study team will collect the samples and transport to designated laboratory.

9. STATISTICAL CONSIDERATIONS

9.1 DETERMINATION OF SAMPLE SIZE

Phase I-dose escalation portion is the IQ 3+3 design, and the phase 1b-portion will be the expansion of each schedule to14 patients for Arms A, B, and at least 12 patients for Arm C. The expected combined sample size for this Phase I study and expanded cohort at the recommended phase 2 dose (RP2D) will be <=40 patients (with >99% probability, based on 800 simulations) for Arms A and B together, with an additional expected 24 patients for Arm C (see below). For arms A and B the sample size will be 28 patients if level 1 has acceptable toxicity on both triplet schedule A and double schedule B.

With 14 patients at the recommended Phase 2 dose for Arms A and B, the DLT rate can be estimated with a SE less than 13.5% and provides added information to refine the recommended phase 2 dose. In addition, with 14 patients, the likelihood of observing at least one patient with PI3K-mTOR-Akt- alteration/PTEN loss (per schedule) is 96% assuming an incidence in the population of 20%. Secondary analysis will also evaluate PFS and response based on molecular subtyping and PI3K-mTOR-Akt/PTEN loss and BRCA mutational status. For Arm C, with a minimum of 12 patients (maximum of 19), the DLT rate can be estimated with a SE less than 14.4%.

At the end of the study, we will have at least 14 patients treated on RP2D for the triplet schedule A and the doublet schedule B, and at least 12 patients treated on the RP2D for the arm/schedule C. Initially, the plan was to facilitate this comparison, when schedules A and B had available slots, by randomizing between schedule A and schedule B. Due to limited time when both arms had slots, and due to prior treatment history which limited patients to one arm, this quasi-randomization proved impractical and slot assignment will be determined based on open slots and treating physician preference. This includes the new added schedule (Arm C). As a result, comparison of response rates across the arms will be on descriptive as these represent different patient populations.

9.2 DETERMINATION OF SAMPLE SIZE FOR ARM C

Sample-size for the triplet Arm C: The starting dose level for schedule C is not the highest possible dose to be tested, which differs from Arm A and B. Once the MTD and recommended phase 2 dose (RP2D) is selected for Arm C, at least 12 total patients will be treated at the RP2D. The expected number of patients (based on 800 simulations with DLT rates of 9.0%, 10.8%, 13.6% and 18.0% or with DLT rates of 6.7%, 7.6%, 9.0% and 10.8% for levels 1-4) is between 17 and 18 patients for dose-finding, and the interquartile range is 15-20 patients.

This is based in the IQ3+3 design. This method has been used in over 10 dose-finding studies to reduce study duration by an average of approximately 23% for a typical Phase I study, with a median increase in the number of patients of 1-4,

while reducing the number of patients turned away due to lack of slots. This method was first presented at JSM 2016, with the manuscript submitted (see below for additional details).

The simulations assume 4 dose levels (-1,1,2,3), starting at dose level 1, with a course length of 28 days, uniform beta distribution for screening of 28 days, a screen failure probability of 30%, an inevaluable rate of 20%, and uniform beta distribution of time to inevaluable over the the 28 day course length, and DLT rates as noted above. The time to DLT event is a beta(1.5,1) distribution over the course length, and the patient inter-arrival has a an exponential distribution with a mean of 10 days.

If after 12 patients have been accrued to the RP2D in total, the number of total patients remains less than 21, additional patients can be accrued to the RP2D (e.g. if the RP2D is dose level 1, with 6 patients treated, and 2 DLTs on dose level 2 for a total 8 patients, 13 additional patients can be added to dose level 1 as opposed to only 6). With 12 patients, any specific severe toxicity with 20% incidence will be observed with 93% probability.

Secondary Objectives: Clinical activity will be described based on the secondary objectives, with a description of the activity based on PD-L1 status. Survival endpoints will be evaluated using Kaplan-Meier methods. Other correlative studies are considered exploratory in the context of this limited Phase I study; however, when the sample size is 12, a single group t-test with a 0.050 one-sided significance level will have 80% power to detect an effect size of 0.766.

9.3 PLANNED EFFICACY EVALUATIONS

Planned efficacy evaluations will include assessment of response (RECIST) and evaluation of progression-free survival. The assessments are specified in the study calendar.

Phase I Operating considerations and methods of analysis

The Phase I design is the IQ 3+3. To evaluate the operating characteristics, we selected 12 different scenarios, and ran 800 simulations. In all scenarios, the probability of selection of any dose as the MTD differed by less than 3% compared to the traditional 3+3, with the majority within 1%. The mean number of DLTs above the MTD for the two designs (3+3 vs IQ 3+3) differed by 0.1 or less. The study duration was reduced by an average of 3.7 months for a standard scenario when implementing the queue-based variation of the 3+3 (the IQ 3+3).

Tables will be created to summarize all toxicities and side effects by grade, attribution, dose, course (cycle 1 vs later cycles), organ and severity. Rates and associated 95% confidence limits will be estimated for DLTs at the RP2D, clinical benefit, response, and PIK3CA mutation rate. Kaplan Meier methods will be used to estimate the median and

95% confidence limits for PFS, EFS, and OS. Descriptive statistics will be provided for the research participant demographics and pharmacokinetic parameters. Subgroup analysis based on correlative biomarkers per secondary endpoints will also be conducted.

10. INVESTIGATOR REQUIREMENTS

10.1 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

10.2 STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both internally by the PI and externally by the COH IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the COH IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

10.3 STUDY MEDICATION ACCOUNTABILITY

The Investigator of the study and City of Hope study team will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62 and Genentech requirements.

All unused remaining product at the end of the study should be disposed of at the study site according to institutional standard operating procedure. If there is no SOP at the site for drug destruction, return study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

10.4 DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the COH IRB.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1 ETHICAL STANDARD

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

11.2 REGULATORY COMPLIANCE

This study is to be conducted in compliance with the IRB approved **protocol** and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- State of California Health and Safety Code, Title 17
- COH policies and procedures

11.3 INSTITUTIONAL REVIEW BOARD

In accordance with City of Hope policies, an Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol and the informed consent form prior to initiation of the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent document will be in the possession of the investigator before the study is initiated.

The IRB will be informed of revisions to other documents originally submitted for review; serious unexpected or unanticipated adverse experiences occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

Any amendment to the protocol document and accompanying informed consent document/template, as developed and provided by the PI, will require review and approval by the COH IRB before the changes are implemented in the study.

11.4 INFORMED CONSENT

The Principal Investigator or IRB approved named designate will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the prospective participant or his/her legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

11.5 PARTICIPANT WITHDRAWAL

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and follow-up procedures.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and follow-up procedures.
- Withdrawal from study treatment, all active procedures, and any future data collection.

11.6 SPECIAL AND VULNERABLE POPULATIONS

11.6.1.1 Inclusion of Women and Minorities

The study is open anyone regardless of gender or ethnicity. Efforts will be made to extend the accrual to a representative population, but in a trial which will accrue approximately 29 participants, a balance must be struck between subject safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the study drugs may have adverse effects on a fetus in uterus.

11.6.1.2 Exclusion of Children

Children (< 18 years old of age) are excluded from this study because the disease does not primarily affect children.

11.6.1.3 Inclusion of HIV Positive Individuals

Participants with a history of HIV are excluded from receiving protocol therapy due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

11.6.1.4 Vulnerable Populations

45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, or economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and COH IRB approval.

11.7 PARTICIPANT CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed participant authorization informing the participant of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information,

ant the rights of a research participant to revoke their authorization for use of their PHI. In the event that a participant revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of participants will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The investigator/institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring/ auditing, IRB reviews, and FDA/regulatory authority inspections. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 FUTURE USE OF SPECIMENS COLLECTED FOR THIS TRIAL

Left-over specimens will be stored for up to 10 years.

11.9 CONFLICT OF INTEREST

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

11.10 FINANCIAL OBLIGATIONS, COMPENSATION, AND REIMBURSEMENT OF PARTICIPANTS

The study drug Ipatasertib will be provided by the manufacturer free of charge to study participants.

The research participant nor the insurance carrier will be responsible for the research procedures related to this study.

The research participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The research participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the research participant were not in a research study.

In the event of physical injury to a research participant, resulting from research procedures, appropriate medical treatment will be available at the City of Hope to the injured research participant, however, financial compensation will not be available.

The research participant will not be paid for taking part in this study.

11.11 PUBLICATION/DATA SHARING

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the City of Hope and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov and results will be reported on ClinicalTrials.gov within 12 months of the estimated or actual completion date of the trial, whichever date is earlier.

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive MPDL3280A treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in **Section 4.6**.

11.12 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

11.13 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated.

The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

11.14 CONFIDENTIALITY

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Genentech representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

12. DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

12.1 SOURCE DOCUMENTS

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.2 DATA CAPTURE METHODS AND MANAGEMENT

Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system. Medidata RAVE is a web based, password protected system that is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

12.3 CASE REPORT FORMS/DATA SUBMISSION SCHEDULE

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be collected using eCRF, and will be submitted according to the timelines indicated in **Table 18**.

Table 18 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 14 calendar days of treatment administration
Adverse Event Report Forms	**Safety lead-in Cycle 1 only**: within 7 calendar days of AE assessment/notification **All other cycles of the safety lead-in and Phase 2**: Within 14 calendar days of the study visit
Response Assessment Forms	Within 10 calendar days of the response assessment

Form	Submission Timeline
Other Assessment Forms (concomitant medications etc.)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of completing treatment or being taken off study for any reason
Follow up/ Survival Forms	Within 14 calendar days of the protocol defined follow up visit date or call

12.4 REGULATORY RECORDS

The investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

13. ADHERENCE TO THE PROTOCOL

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. Protocol deviations may be on the part of the subject, the investigator, or study staff.

All deviations from the protocol must be documented in study subject source documents and promptly reported. The Study PI will report the deviation according to City of Hope's deviation policy for reporting deviations (See **Section 6.1**).

14. STUDY OVERSIGHT, QUALITY ASSURANCE, AND DTA & SAFETY MONITORING

14.1 ALL INVESTIGATOR RESPONSIBILITIES

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

All investigators agrees to:

- Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when necessary to protect the safety, rights or welfare of subjects.
- Personally conduct or supervise the study (or investigation).
- Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
- Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.

- Promptly report to the IRB and the Sponsor all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- Seek IRB and Sponsor approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

Site Lead Investigator Responsibilities

The Site Lead Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations (CFR). The Site Lead Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

It is the responsibility of the Site Lead Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events, deviations, and unanticipated problems.

The Site Lead Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms at his/her site. For remote or onsite monitoring and auditing, the Site Lead Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Site Lead Investigator and will require his/her final signature to verify the accuracy of the data.

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of participants under the investigator's care; and for the control of drugs under investigation.

14.2 STUDY PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities as defined in § 21 CFR 312.

14.3 PROTOCOL MANAGEMENT TEAM (PMT)

Safety assessments will consist of monitoring and reporting adverse events and serious adverse events per protocol. This includes all events of death and any study-specific issue of concern (see **Section 6.1**).

14.4 MONITORING/AUDITING

Clinical site monitoring/auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring/ auditing for this study will be performed by the City of Hope Office of Clinical Trials Auditing and Monitoring (OCTAM).

Documentation of monitoring/auditing activities and findings by OCTAM will be provided to the study team, the PI, and the COH DSMC.

14.5 CITY OF HOPE DATA AND SAFETY MONITORING COMMITTEE

The DSMC is a multidisciplinary committee charged with overseeing the monitoring of safety of participants in clinical trials, and the conduct, progress, validity, and integrity of the data for all clinical trials that are sponsored by City of Hope. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. The committee reviews the progress and safety of all active research protocols that are not monitored by another safety and data monitoring committee or board.

The COH DSMC will review and monitor toxicity and accrual data from this trial. Information that raises any questions about participant safety will be addressed with the PI, statistician and study team.

Refer to Data & Safety Monitoring Plan, Adverse Event and Unanticipated Problem Reporting **Section 6** for details.

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Appendix 1 Study Calendar

	Screening [a] Days –28 to 0	Treatment Cycles (28-day cycles)								EOT[b]	Follow-Up
		C1D1± 3d	C1D8± 3d	C1D15± 3d	C2D1± 3d	C2D8± 3d	C2D15± 3d	C3D1± 3d	C4D1±3d+	≤ 30d of Last Dose	
Informed consent	x [c]										
Demographics	x										
Medical history	x										
EORTC QLQ-C30	x	x	C4D1, every 3 cycles [d]							x	x
Vital signs	x	x	x	x	x	x	x	x	x	x	
Weight	x	x			x			x	x	x	
Height	x										
Physical exam	x	x		x	x		x	x	x	x	
ECOG	x	x		x	x		x	x	x	x	
ECG [e]	x	Clinically indicated									
Echocardiogram	x										
CBC Diff, CMP [f]	x	x	x	x	x		x		x	x	
Amylase, lipase, thyroid function [g]	x	x						x[g]		x	
Pregnancy test [h]	x										
INR, aPTT	x									x	
Hepatitis B &C, HIV serology [i]	x										
Fasting lipid/A1c [j]	x								x	x	
Urinalysis	x	Clinically indicated									
Peripheral Blood Biomarkers [k]		x			x				C4D1	x	
Stool microbiome, Calprotectin [l]	x								C4D1	x	

	Screening [a] Days –28 to –1	Treatment Cycles (28-day cycles)								EOT[b] ≤ 30d of Last Dose	Follow-Up
		C1D1± 3d	C1D8± 3d	C1D15± 3d	C2D1± 3d	C2D8± 3d	C2D15± 3d	C3D1± 3d	C4D1±3d+		
Tumor tissue [m]	x				X					X	
Tumor Staging [n]	x	x [o]									
Con-meds [p]	x	x	x	x	x	x	x	x	x	x	
Adverse events [q]	x	x	x	x	x	x	x	x	x	x	x
Study treatment [r]		x	x	x	x	x	x	x	x		
Survival FU											x [s]
Patient Diary [t]		x			x			x	x		

Notes:* On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Patient will have **MD visits on Days 1, 15 of cycle 1 & 2**, then day 1 of each following cycles. **Additional study nurse visit on Day8 of C1 & 2 for AE assessment.**

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 1 may be used; such tests do not need to be repeated for screening. Staging CT/PET-CT/bone scan/MRI brain can be used if performed within **35 days** prior to Day1Cycle1.

[b] End of treatment visit (EOT): Patients who discontinue study treatment will return to the clinic for a treatment discontinuation visit not more than 30 days after the last dose of study treatment. The visit at which response assessment shows progressive disease may be used as the treatment discontinuation visit.

[c] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[d] EORTC QLQ-C30 questionnaire will be completed on **C1D1, then every 3 cycle at the tumor assessment visit,** before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Patients who discontinue study treatment for any reason other than progressive disease or loss of clinical benefit will complete the EORTC QLQ-C30 at each tumor assessment visit, until radiographic disease progression per RECIST v1.1 or loss of clinical benefit determined by treating physician or study investigator. All patients will complete the EORTC QLQ-C30 at **3 and 6 months** after radiographic disease progression per RECIST v1.1 or (for ipatasertib-treated patients who continue treatment after radiographic disease progression) loss of clinical benefit as determined by the investigator.

[e] ECG recordings will be obtained during screening and as clinically indicated at other timepoints. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings.

[f] Screening laboratory test results must be obtained within 14 days prior to initiation of study treatment. If screening laboratory assessments were performed within **96 hours prior to** Day 1 of Cycle 1, they do not have to be repeated. CBC, diff and CMP will be drawn on days 1,8,15 of each cycle.

[g] Amylase, lipase, and thyroid function test should be checked **every other cycle**.

[h] All women of childbearing potential will have a serum pregnancy test within **96 hours** prior to initiation of study drug, HCG does not need to be repeated thereafter.

[i] At screening, patients will be tested for HBsAg, HBsAb, total HBcAb, and HCV antibody, as well as HIV serology. If a patient has a negative HBsAg test and a positive total HBcAb test at screening, an HBV DNA test should be performed. If a patient has a positive HCV antibody test at screening, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.

[j] Fasting lipid profile and HbA_{1c} will be assessed at screening, **every 3 cycles** starting on Day 1 of Cycle 4, and at end-of-study visit.

[k] Peripheral blood samples will be collection for biomarker correlatives will be collected at **C1D1, C2D1, C4D1 and end-of-treatment visit**: 1 green top, 1 Streck tube (Cell-free DNA BCT®) and 1 lavender top.

[l] Stool samples will be collected at: **baseline (within 7 dyas), C4D1(+/- 3 days) and end-of-treatment visit**.

[m] If archival tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria. Refer to **Section 4.5**. for tissue sample requirements. Patients will undergo tumor biopsy sample collection, if deemed clinically feasible by the investigator, at the time of first evidence of radiographic disease progression per RECIST v1.1. Biopsies should be performed within 40 days after progression or prior to the next anti-cancer therapy, whichever is sooner. See **Section 4.5**. for tissue sample requirements.

[n] All measurable and evaluable lesions should be assessed and documented at screening. Tumor assessments performed as standard of care prior to obtaining informed consent and **within 35 days** prior to initiation of study treatment do not have to be repeated at screening. **Screening assessments must include CT scans (with oral or IV contrast), bone scan and MRI Brain (or CT of brain with contrast if MRI is contraindicated).** If a CT scan with contrast is contraindicated (i.e., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans of the abdomen, pelvis, and head should be performed. An MRI scan of the head is required to confirm or refute the diagnosis of CNS metastases at baseline in the event of an equivocal CT scan. On study **bone scans and CT scans of the neck should also be performed if clinically indicated.** At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may be used. Restaging scans are repeated every 3 months or 12 weeks.

[o] Patients will undergo tumor assessments at baseline, **every 12 weeks or 3 cycles** until radiographic disease progression per RECIST v1.1 OR loss of clinical benefit as determined by the investigator. Thus, tumor assessments are to continue according to schedule in patients who discontinue treatment for reasons other than disease progression or loss of clinical benefit.

All measurable and evaluable lesions should be re-assessed at each subsequent tumor evaluation. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans).

[P] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 14 days prior to initiation of study treatment until the treatment discontinuation visit.

[q] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 30 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first, and serious adverse events and adverse events of special interest will continue to be reported until 90 days after the last dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first. After this period, all deaths, regardless of cause, should be reported. In addition, Genentech, Inc. should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study treatment (see Appendix 3). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

[r] The initial dose of ipatasertib will be given with the witness of study team. Carboplatin and paclitaxel infusion will be delivered per current FDA package insert. If an infusion reaction occurs, subsequent infusion can be given with extended infusion time per institutional practice and guidance from pharmacy. For dosing regimen, see **Section 3.1**. Ipatasertib will be given at a starting dose of 400mg oral daily for 28 days. Carboplatin will be given at a starting dose of AUC2 on days 1, 8, 15 every 28 days for Triplet Schedule A. Paclitaxel will be given at a dose of 80 mg/m2 administered by IV infusion on days 1,8,15 of every 28 day cycles for Triplet Schedule A. Carboplatin will be given at a starting dose of AUC 2 on days 1, 8, 15 of 28 day cycles for doublet schedule B.

[s] After treatment discontinuation, information on survival follow-up and new anti-cancer therapy (including targeted therapy and immunotherapy) will be collected via telephone calls, patient medical records, and/or clinic visits approximately every 3 months (unless the patient withdraws consent or the Investigator terminates the study). If a patient requests to be withdrawn from follow-up, this request must be documented in the source documents and signed by the investigator. If the patient withdraws from study, the study staff may use a public information source (e.g., county records) to obtain information about survival status only.

[r] Patient diary will be distributed to patients on day 1 each cycle, need to be filled by patient and returned to study team on day 1 of each following cycle and each MD/study nurse visit.

Appendix 2 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Source: Gault MH, Longerich LL, Harnett JD, *et al*. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992; 62:249.

Appendix 3
Genentech Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

Appendix 4
FDA MedWatch 3500 Form

This form is downloadable at the following site:

https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/forms/ucm048334.pdf

Appendix 5
Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE 5.0)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 6
Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer *et al.* 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[1]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval $\leq$ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be $\geq$ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be $\leq$ 5 mm). At baseline and follow-up, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

[1] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start 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 the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

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

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be utilized for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered non-pathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non–lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non–lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non–lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to <10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters on study (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Appendix 6 Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Appendix 6 Table 2 is to be used.

Appendix 6 Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Appendix 6 Table 2 Criteria for Overall Response at a Single Timepoint: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and

during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target lesions as shown in Appendix 6 Table 1 and Appendix 6 Table 2.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

REFERENCE:

Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.

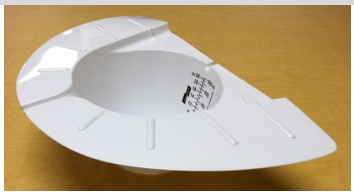
Appendix 7
Stool Collection Kit General Instructions

As a part of your participation in the current study, we have some specific instructions related to collection of stool. Please abide by these instructions, as they are essential for the proper conduct of the study.

You are being asked to collect samples at the following times: Day-7 to Day -1 of Cycle 1 Day 1; Cycle 4 Day 1 (+/- 7 days); End of treatment (+/-7 days)

Before you begin, review the following:

a. Make sure you have a collection hat and collection tube.
b. Make sure you are able to deliver the sample to City of Hope within 1 week.

STEP 1: Please place the *collection hat* around the rim of your toilet seat for stool collection.  	
STEP 2: Unscrew the collection tube cap and use the spoon to scoop one spoonful of feces (about the size of a quarter) from a sample. Place the sample in the collection tube. Tighten the cap and shake to mix the contents thoroughly (invert 10 times) to create a suspension. Note: Some fecal material may be difficult to re-suspend. As long as the material is suspended, the sample is stabilized. Foaming/frothing during shaking is normal.	 Scoop a portion of the stool sample into the DNA/RNA Shield™ Fecal Collection Tube
STEP 3: Wash hands well, and write today's date on the label.	
STEP 4: Place the plastic tube in the bag, and seal the back using the adhesive tape already present on the bag.	
STEP 5: Bring the sample to your City of Hope appointment.	THANK YOU FOR YOUR PARTICIPATION!

An At-Home Sample Collection kit will be provided by the study team:

Contents of each kit to be provided to participants for at home collection:

[] Copy of Appendix 7: Instructions for Stool Specimen Collection

[] Stool collection hat

[] Specimen tube with label attached

Label should have participant identifier added; the participant will be asked to add the date himself/herself.

[] Plastic sealable bag

Appendix 8
Diet and Bowel Movement Log

As a part of your participation in the current study, we are requesting that you complete a study log every day.

- When you come to the clinic, bring your logs with you.
- Each page has room for seven days – one row should be completed for each day.
- Please avoid dietary changes: any NEW intake of yogurt, yogurt-containing foods, and/or other bacteria-fortified foods.

Example of how the top part of the log will look:

- A study team member will complete the information in this box before you leave the clinic.

COMPLETED BY STUDY TEAM	Participant Initials: JSM	Participant Research Number: 1001	Group: A

Example of how the information you enter might look:

- You or someone close to can complete the log for you, so long as the information is correct.
- List anti-diarrhea medication taken.
- The person who completes that day's entry should write his or her initials in the last column.

Day and Date	General description of food I ate:	*Did I eat yogurt or take probiotics?*	*How was my stool frequency?*	*Was a stool sample collected?*	*Medications taken*	*Initials of person filling information*
	Eggs, toast, juice Ham sandwich, coke, potato chips Steak, mashed potatoes, wine	○ Yes ☒ No	☒ Seems like baseline ○ 1-3 stools more than baseline ○ 4-6 stools more than normal ○ 7 or more than baseline, or incontinence	○ Yes ☒ No	Vitamin C, Lipitor	JBC
			○ Seems like baseline			

Example of the signature line:

- When you hand over the document to the study team, they will ask to sign and date at the bottom of each log if you agree that the information is complete and correct.

At the time of handing over the document -- Participant Signature: Joseph Black Smith Date 12/18/2002

Date	Description of food	*Yogurt probiotics?*	*Stool frequency*	*Initials of person filling information*
		◯ Yes ◯ No	◯Seems like baseline ◯1-3 more than baseline ◯4-6 more than normal ◯7 or more than baseline, or incontinence	
		◯ Yes ◯ No	◯ Seems like baseline ◯1-3 stools more than baseline ◯4-6 stools more than normal ◯7 or more than baseline, or incontinence	
		◯ Yes ◯ No	◯ Seems like baseline ◯1-3 stools more than baseline ◯4-6 stools more than normal ◯7 or more than baseline, or incontinence	
		◯ Yes ◯ No	◯ Seems like baseline ◯1-3 stools more than baseline ◯4-6 stools more than normal ◯7 or more than baseline, or incontinence	
		◯ Yes ◯ No	◯ Seems like baseline ◯1-3 stools more than baseline ◯4-6 stools more than normal ◯7 or more than baseline, or incontinence	
		◯ Yes ◯ No	◯ Seems like baseline ◯1-3 stools more than baseline ◯4-6 stools more than normal ◯7 or more than baseline, or incontinence	
		◯ Yes ◯ No	◯ Seems like baseline ◯1-3 stools more than baseline ◯4-6 stools more than normal ◯7 or more than baseline, or incontinence	

Participant Signature: ________________________________Date _________

Appendix 9
Oral Medication Pill Diary

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

Study drug Instructions – When and How:

- Take ipatasertib **once a day** with water
- Take capecitabine twice a day per prescription with water
- Swallow pills; do not chew them or crush them
- Take the drugs at approximately the same time each day with or without food
- Do not skip any doses

What if I miss a scheduled dose?

- If **less than 8 hours** have passed from the scheduled time, then **take the missed dose** as soon as you remember.
- If more than 8 hours have passed from the scheduled time, then skip the missed dose. Wait for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What if I vomit a dose?

- If you vomit your pills, write this down in your pill diary.
- Wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Additional Instructions:

- Keep your study drug in the original container until you take it.
- Do NOT throw away empty pill bottles or unused pills.
- Bring this diary, all pill bottles, and any unused pills to each clinic visit.
- Contact your study team if you are having any new or worsening side effects.

Contact Information for Study Nurse

Phone:

Name:

How to fill the Pill Diary (Example Only)

To be filled by study team *# of pills to take: 1*

Participant Only	***Week 1***						
	Cycle Day	*Week Day*	*Date*	*Time*	*Dose of Ipatasertib*	*Dose of Capecitabine*	*Immodium/Other Anti-diarrhea Meds*
	1	*Mon*	*4/10/17*	*10:10 AM*	*1*		*2*
	2	*Tues*	*4/11/17*	*10:30 AM*	*1*		*1*

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

To be filled by study team # of Ipatasertib pills to take:_____

Week 1						
Cycle Day	**Week Day**	**Date**	**Time**	**Dose of Ipatasertib**	**Dose of Capecitabine**	**Immodium/Other Anti-diarrhea Medication**
1			___:___AM/PM			
2			___:___AM/PM			
3			___:___AM/PM			
4			___:___AM/PM			
5			___:___AM/PM			
6			___:___AM/PM			
7			___:___AM/PM			

To be filled by study team # of Ipatasertib pills to take:_____

Week 2						
Cycle Day	**Week Day**	**Date**	**Time**	**Dose of Ipatasertib**	**Dose of Capecitabine**	**Immodium/Other Anti-diarrhea Medication**
8			___:___AM/PM			
9			___:___AM/PM			
10			___:___AM/PM			
11			___:___AM/PM			
12			___:___AM/PM			
13			___:___AM/PM			
14			___:___AM/PM			

Participant Signature *(please sign when submitting your diary)*	**Date:**
_____	____/_____/_____

Subject ID#:	Patient Initials (F, M, L):	
Institution:	Cycle #:	Cycle start date:

To be filled by study team # of Ipatasertib pills to take:_____

Week 3						
Cycle Day	**Week Day**	**Date**	**Time**	**Dose of Ipatasertib**	**Dose of Capecitabine**	**Immodium/Other Anti-diarrhea Medication**
15			___:___AM/PM			
16			___:___AM/PM			
17			___:___AM/PM			
18			___:___AM/PM			
19			___:___AM/PM			
20			___:___AM/PM			
21			___:___AM/PM			

To be filled by study team # of Ipatasertib pills to take:_____

Week 4						
Cycle Day	**Week Day**	**Date**	**Time**	**Dose of Ipatasertib**	**Dose of Capecitabine**	**Immodium/Other Anti-diarrhea Medication**
22			___:___AM/PM			
23			___:___AM/PM			
24			___:___AM/PM			
25			___:___AM/PM			
26			___:___AM/PM			
27			___:___AM/PM			
28			___:___AM/PM			

Participant Signature *(please sign when submitting your diary)* _____	**Date:** ____/_____/_____

Study Team ONLY**: # of Ipatasertib Pill Bottles Returned: _____ # of Pills Returned: _____**
*Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles o the # of pills returned), please reconcile (initials & date):*_____

Study Team ONLY**: # of Capecitabine Pill Bottles Returned: _____ # of Pills Returned: _____**
*Compare with drug diary entries made by participant/guardian. If there is a discrepancy (in the # of bottles o the # of pills returned), please reconcile (initials & date):*_____

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Appendix 10
Biospecimen Sample Transportation Guidelines

If out-of-State shipping required, please f follow the requirements for the proper packaging and shipping of biomedical material found in 42 CFR Part 72 - Interstate Shipment of Etiologic Agents Centers for Disease Control and Prevention, Office of Health and Safety Biosafety Branch.

1. **Samples must be de-identified with no PHI.** Aim to ship samples on a **Monday through Thursday**. If this is not feasible, advance arrangements should be made with Dr. Stewart (dapstewart@coh.org) and Dr. Susan Yost (suyost@coh.org). Notify Dr. Stewart and Dr. Yost of impending shipment. Billing information can be requested at that time. Also, on the day of shipment, please email recipient the sample shipment information and a sample manifest.
2. **Peripheral Blood Samples:** ship to:

   Dr. Tim Synold
   Cc: Lesley Smith-Powell
   Analytical Pharmacology Core Facility (APCF)
   Shapiro 1042
   City of Hope National Medical Center
   1500 E. Duarte Road
   Duarte, CA 91010
   Tel: 626-218-2954
   Emails: tsynold@coh.org; Lsmith-Powell@coh.org

3. **Pathology Slides/Blocks:**

   Batch ship with frozen gel ice-packs in order to prevent the melting of paraffin-embedded tissue blocks during transit to:

   Dr. Susan Yost
   Department of Medical Oncology & Therapeutic Research
   Building 51, City of Hope National Medical Center
   1500 East Duarte Rd, Duarte, CA 91010
   Direct: 626-218-0499 Internal x 80499
   Email: suyost@coh.org

4. **Microbiome specimens: See Appendix 7 and 8 for stool collection:**

   Dr. Cui Ke
   CC: Biospecimen Coordinator Biospecimen Coordinator
   COH Biorepository Core
   City of Hope National Medical Center
   1500 E. Duarte Road
   Duarte, CA 91010
   626-218-1848; 626-218-0462
   kcui@coh.org; spathan@coh.org

Approximately 30-50 samples stool samples will be temporarily stored at -80°C in the Analytical Pharmacology Core Facility (APCF) in Shapiro 1042 (Dr. Tim Synold/Leslie Smith-Powell) until batch shipped to TGen:

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Appendix 11
EORTC QLQ-C30

The EORTC QLQ-30 Forms and Scoring were downloaded with permission for the following websites:

QLQ-C30 Core Questionnaire in Armenian
http://www.eortc.be/qol/files/C30/QLQ-C30%20Armenian.pdf

QLQ-C30 Core Questionnaire in Chinese
http://www.eortc.be/qol/files/C30/QLQ-C30%20Chinese%20Mandarin%20(China).pdf

QLQ-C30 Core Questionnaire in English
http://www.eortc.be/qol/files/C30/QLQ-C30%20English.pdf

QLQ-C30 Core Questionnaire in Spanish
http://www.eortc.be/qol/files/C30/QLQ-C30%20Spanish%20(Spain).pdf

QLQ-C30 Scoring Manual
http://www.eortc.be/qol/files/SCManualQLQ-C30.pdf