Clinical Study Protocol-

A MULTICENTER, OPEN-LABEL, NON-COMPARATIVE, THREE-ARM, PHASE IIa TRIAL OF IPATASERTIB (GDC-0068) IN COMBINATION WITH NON-TAXANE CHEMOTHERAPY AGENTS FOR TAXANE-PRETREATED UNRESECTABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER PATIENTS (PATHFINDER)

Code: MEDOPP253_PATHFINDER

Drug Tested:	Ipatasertib (GDC-0068)èp
EudraCT#:	2018-004648-44
Clinical Trials.gov#:	NCT04464174
Protocol#:	MEDOPP253
Protocol Date:	27-Apr-2023

PROTOCOL REVIEW HISTORY

- CSP: Version 1.0, 30-Sep-2019
- CSP: Version 2.0, 18-May-2020 (only Spain)
- CSP: Version 2.1, 15-Jun-2020 (only Portugal)
- CSP: Version 3.0, 20-Sep-2021
- CSP: Version 4.0, 04-Apr-2022
- CSP:Version 5-0, 27-Apr-2023

SPONSOR'S SIGNATURE PAGE

Study title: A Multicenter, Open-Label, Non-Comparative, Three-Arm, Phase IIa Trial of Ipatasertib (GDC-0068) in Combination with Non-Taxane Chemotherapy Agents for Taxane-Pretreated Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Patients (PATHFINDER)

Study code: MEDOPP253

Version number: 5.0 **Version date:** 27-Apr-2023

[redacted]	[redacted]	05/05/2023
Sponsor's Medical Scientist	Signature	Signature date (DD-Mmm-YYYY)
[redacted]	[redacted]	11/05/2023
Scientific Global Coordinator	Signature	Signature date (DD-Mmm-YYYY)

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PATHFINDER Study Investigators	

DECLARATION OF INVESTIGATORS

Protocol Title: A Multicenter, Open-Label, Non-Comparative, Three-Arm, Phase Iia Trial of Ipatasertib (GDC-0068) in Combination with Non-Taxane Chemotherapy Agents for Taxane-Pretreated Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Patients (PATHFINDER)

I have received, reviewed and understood the following:

a) Protocol version: 5.0, dated 27-Apr-2023

b) Investigator's Brochure (IB) of ipatasertib (GDC-0068) and Summary of Product Characteristics (SmPC) for capecitabine, carboplatin, and gemcitabine with details of clinical and nonclinical data that are relevant to the study of the products in human subjects.

- I have been adequately informed about the development of the investigational products to date. I will confirm the receipt of updated IB and SmPCs. I have read this study protocol and agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol.
- I fully understand that any changes instituted by the investigator(s) without previous agreement with the Sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study patients (other than those procedures necessary for the wellbeing of the patients). I am aware that I cannot deviate from or apply changes to the protocol without prior approval or the favorable opinion of the Institutional Review Board (IRB) or Ethics Committee (EC) and/or before Sponsor's agreement to avoid immediate risk to the trial patients. If this occurs, I agree to inform the Sponsor as to the deviation or changes in writing and their reasons, as soon as possible.
- I will not enroll the first patient in the study until I have received approval from the appropriate IRB/EC and until all legal and regulatory requirements in my country have been fulfilled.
- The study will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and its amendments, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (ICH E6(R2) GCP) and applicable regulations and laws.
- I agree to obtain, in the manner described in this protocol and in (ICH E6(R2) GCP), signed informed consent form (ICF) by the patient or witnessed verbal ICF to participate for all patients whose participation in this study is proposed to and before any patient's study specific procedure is done.

- I will ensure that the study drug(s) supplied by the Sponsor are being used only as described in this protocol.
- I am aware of the requirements for the correct reporting of serious adverse events, and I commit to document and to report such events as required by the Sponsor and in accordance with Health Authority Regulatory requirements.
- I agree to supply – upon request – the Sponsor or Sponsor's representative with evidence of current laboratory accreditation, the name and address of the laboratory, and a list of normal values and ranges.
- I agree with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.
- I agree to keep all source documents and case report forms as specified in the relevant sections of this protocol.
- I will provide all required Regulatory Authority forms, up-to-date curriculum vitae of myself, sub-investigators and of any member of my study team (if requested) before the study starts, which may be submitted to regulatory authorities.
- I am aware of the possibility of being audited by the Sponsor or its delegate or inspected by regulatory authorities for the performance of this study. I will permit monitoring, auditing and inspection and provide direct access to source data/documents and reports for these purposes.
- Furthermore, I confirm herewith that the Sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to Health Authorities worldwide.

Name: _____

Signature: _____ Date: _____

TABLE OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse events of special interest
AKT	Serine/threonine kinase B
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
AUC	Area under the curve
BL	Basal-like
BLBC	Basal-like breast cancer
BRCA1	*Breast Cancer 1*
BSA	Body surface area
CAP	College of American Pathologists
CBR	Clinical benefit rate
cfDNA	Cell-free DNA
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CRO	Clinical Research Organization
CT	Computerized tomography
DDI	Drug-Drug Interaction
DILI	Drug Induced Liver Injury
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram

ECHO	Echocardiogram
ECOG	Eastern European Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
EoS	End of study
EoT	End of Treatment
ER	Estrogen receptor
ESA	Erythropoiesis-stimulating agents
FDA	Food and Drug Administration
FFPE	Formalin-fixed and paraffin-embedded
G-CSF	Granulocyte-colony stimulating factors
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HbA1c	High hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human Epidermal Growth Factor Receptor 2
HL	Hy's Law
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMP	Investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional Review Board
ISH	*In situ* hybridization
ITT	Intention-to-treat

LAR	Luminal androgen receptor
LPLV	Last patient, last visit
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
mCRPC	Metastatic castration resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MSL	Mesenchymal stem-like
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
mTORC	Mammalian target of rapamycin complex
MUGA	Multiple gated acquisition
NCCN	National Comprehensive Cancer Network
NGS	Next-generation sequencing
ORR	Objective response rate
OS	Overall survival
PARP	Poly(ADP-Ribose)Polymerase
pCR	Pathological complete response
PCR	Polymerase chain reaction
PHL	Potential Hy's Law
PD	Progressive disease
PD-L1	Programmed death ligand 1
PDK1	Phosphoinositide-dependent kinase 1
PET	Positron emission tomography
PFS	progression-free survival
PgR	Progesterone receptor

PI3K	Phosphoinositide 3-kinase
PIK3CA	p110α catalytic subunit of PI3K
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
PP	Per-Protocol
PR	Partial response
PTEN	Phosphatase and tensin homolog
PTT	Partial Thromboplastin Time
SAE	Serious adverse event
SD	Stable disease
SmPC	Summary of Product Characteristics
TBL	Total bilirubin
TIL	Tumor-infiltrating lymphocyte
TNBC	Triple-Negative Breast Cancer
TTR	Time to response
ULN	Upper limit of normal
UPN	Unique patient number
VEGF	Vascular-Endothelial Growth Factor
WBC	White blood cell

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LIST OF APPENDICES

1 PROTOCOL SYNOPSIS

Investigational Medicine Products	Ipatasertib (GDC-0068)
Protocol Number	MEDOPP253
EudraCT Number	2018-004648-44
Protocol Title	A Multicenter, Open-Label, Non-Comparative, Three-Arm, Phase IIa Trial of Ipatasertib (GDC-0068) in Combination with Non-Taxane Chemotherapy Agents for Taxane-Pretreated Unresectable Locally Advanced or Metastatic Triple-Negative Breast Cancer Patients (PATHFINDER)
Target Disease	Hormone Receptor (HR)-negative/Human Epidermal Growth Factor Receptor 2 (HER2)-negative unresectable locally advanced or metastatic breast cancer (MBC).
Patients	Women age ≥ 18 years with triple-negative unresectable locally advanced or MBC that is not amenable to resection with curative intent. Patients must have received at least one, but not more than two, prior chemotherapeutic regimens for treatment of unresectable locally advanced and/or metastatic disease (at least one regimen must have contained a

	taxane). Earlier adjuvant or neoadjuvant therapy for more limited disease will be considered as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. Therefore, exclusive prior taxane-based therapy as adjuvant or neoadjuvant treatment is also allowed if the patient had a disease-free interval of less than 12 months after completing this treatment. Patients are not eligible if they have received previous treatment with phosphatidylinositol 3-kinase (PI3K), and/or mammalian target of rapamycin (mTOR), and/or AKT inhibitors. Evidence of either measurable or evaluable disease (as for Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v.1.1]) is mandatory, with at least a site of disease amenable to biopsy. Patients with bone-only metastases are also eligible.
Number of patients	54 patients.
Study objectives	**Primary objective:** To evaluate the safety and tolerability of ipatasertib (GDC-

	0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine in the intention-to-treat (ITT) population of patients with taxane-pretreated unresectable locally advanced or metastatic triple-negative breast cancer (TNBC). **Secondary objectives:** To determine the efficacy of ipatasertib (GDC-0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine in the ITT population and in each treatment arm. **Exploratory objectives:** • [redacted] • [redacted]

	• [redacted]
Study endpoints	**Primary endpoint:** • Incidence of adverse events (AEs) as assessed by the investigator, with severity determined through the use of US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0. **Secondary endpoints:** • Progression-free survival (PFS), defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined locally by the investigator through the use of RECIST v.1.1. • Time to response (TTR), defined as the time from the treatment initiation to time of the first objective

	tumor response (tumor shrinkage of ≥ 30%) observed for patients who achieved a complete response (CR) or partial response (PR), as determined locally by the investigator through the use of RECIST v.1.1. • Objective response rate (ORR), defined as a CR or PR as determined locally by the investigator through the use of RECIST v.1.1. • Duration of response (DoR), defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined locally by the investigator through use of RECIST v.1.1. • Clinical benefit rate (CBR), defined as an objective response (CR or PR), or stable disease (SD) for at least 24 weeks, as determined locally by the investigator through the use of RECIST v.1.1. • Overall survival (OS), defined as the time from treatment initiation to death from any cause, as

	determined locally by the investigator through use of RECIST v.1.1. • Best percentage of change from baseline in the size of target tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, as determined locally by the investigator through use of RECIST v.1.1. **Exploratory endpoints:** • PFS, TTR, ORR, DoR, CBR, OS, and best percentage of change in target tumor lesions determined locally by the investigator through the use of RECIST v.1.1 in the subset of patients with [redacted] altered tumors. • Relationship between tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS). • Changes in mutation and copy number in oncogenes, tumor

	suppressors, and/or other genes associated with disease progression assessed by deoxyribonucleic acid (DNA) sequencing. • Changes in levels of tumor suppressors, immune checkpoints, mitotic index, apoptotic index, and/or immune-cell infiltration assessed by immunohistochemistry (IHC). • Associations of breast cancer subtypes defined by molecular signatures with patient outcomes.
Type of study	This is a multicenter, open-label, non-comparative, three-arm, phase IIa clinical trial with safety run-in.
Selection criteria	**Inclusion criteria:** Patients must meet **ALL** of the following inclusion criteria to be eligible for enrolment into the study: 1. Signed informed consent form (ICF) prior to participation in any study-related activities. 2. Female patients ≥ 18 years at the time of signing ICF.

	3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1. 4. Life expectancy of ≥ 12 weeks. 5. Histologically confirmed TNBC per American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) criteria based on local testing on the most recent analyzed biopsy. Triple-negative is defined as <1% expression for estrogen receptor (ER) and progesterone receptor (PgR) and negative for human epidermal growth factor receptor 2 (HER2) (0–1+ by IHC or 2+ and negative by *in situ* hybridization [ISH) test]. 6. Unresectable locally advanced or metastatic disease documented by computerized tomography (CT) scan or magnetic resonance imaging (MRI) that is not amenable to resection with curative intent. 7. Measurable or evaluable disease as per RECIST v.1.1. Patients with bone-only metastases are also eligible. 8. Refractory to or relapsed after one or two prior standard of care chemotherapy regimens for unresectable locally

	advanced or MBC. Earlier adjuvant or neoadjuvant therapy for more limited disease will be considered as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. *Note: Exclusive tumor marker elevation will not be considered sufficient for diagnosis of disease progression.* 9. Prior therapy must have included a taxane in any combination or order and either in the early, locally advanced, or metastatic setting. *Note: Exclusive prior taxane-based therapy as adjuvant or neoadjuvant treatment is also allowed if the patient had a disease-free interval of less than 12 months after completing this treatment.* 10. Eligible for one of the chemotherapy options (capecitabine, eribulin, carboplatin plus gemcitabine) as per local investigator assessment and slots availability. Patients treated with (neo)adjuvant platinum

	salts or capecitabine and who have relapsed more than one year after the last dose of either treatment may be allowed to be included in the treatment arms based on ipatasertib (GDC-0068) in combination with carboplatin plus gemcitabine and capecitabine, respectively. 11. Previous treatment with androgen receptor antagonists, poly ADP-ribose Polymerase (PARP) inhibitors, and immunotherapy is allowed. Those patients who have previously received a PARP inhibitor will not be included in the carboplatin and gemcitabine arm unless PARP inhibitors were used in the early breast cancer setting and the period between the end of PARP inhibitor-based regimen and onset of metastatic disease is at least of 12 months. 12. Resolution of all acute toxic effects of prior anti-cancer therapy to grade ≤ 1 as determined by the NCI-CTCAE v.5.0 (except for alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

	13. Willingness and ability to provide a tumor biopsy from a metastatic site or the primary breast tumor at the time of the inclusion in order to perform exploratory studies. If not feasible, patient eligibility should be evaluated by a Sponsor's qualified designee. *Note: Subjects for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) may submit an archived metastatic tumor specimen only upon agreement from the Sponsor.* 14. Patients agree to give blood samples (liquid biopsy) at the time of inclusion, after two cycles of study treatment, and upon progression or study termination. 15. Adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, defined by the following: a) Hematological: White blood cell (WBC) count > 3.0 x 10^9/L, absolute neutrophil count (ANC) > 1.5 x 10^9/L, platelet count > 100.0 x10^9/L, and hemoglobin > 9.0 g/dL. b) Hepatic: Serum albumin ≥ 3 g/dL; Bilirubin ≤ 1.5

	times the upper limit of normal (× ULN) (≤ 3 x ULN in the case of Gilbert's disease); aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 × ULN (in the case of liver metastases ≤ 5 × ULN); alkaline phosphatase (ALP) ≤ 2 × ULN (≤ 5 × ULN in the case of liver and/or bone metastases). c) Renal: Serum creatinine < 1.5 × ULN or creatinine clearance ≥ 50 mL/min based on Cockcroft−Gault glomerular filtration rate estimation. d) Coagulation: Partial Thromboplastin Time (PTT) (or activated Partial Thromboplastin Time [aPTT]) and International Normalized Ratio (INR) ≤ 1.5 × ULN (except for patients receiving anticoagulation therapy). *Note: Patients receiving heparin treatment should have a PTT (or aPTT) ≤ 2.5 × 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 one to four days apart. Patients should be on a stable anticoagulant regimen. 16. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse), or to use a highly effective non-hormonal form of contraception, or two effective forms of contraception, as defined in the protocol during the treatment period and for at least 28 days after the last dose of ipatasertib (GDC-0068), three months after the last dose of eribulin, and six months after the last dose of carboplatin and gemcitabine or capecitabine, whichever occurs later, and agreement to refrain from donating eggs during this same period. Women of childbearing potential must have a negative serum pregnancy test before study treatment initiation. **Exclusion criteria:**

	Patients will be excluded from the study if they meet **ANY** of the following criteria: 1. Inability to comply with study and follow-up procedures. 2. Previous treatment with PI3K, mTOR, or AKT inhibitors. 3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (e.g., radiotherapy, stereotactic surgery), are clinically stable, and off anticonvulsants and steroids for at least two weeks before first dose of study treatment. 4. Radiotherapy or limited-field palliative radiotherapy within seven days prior to study enrolment, or patients who have not recovered from radiotherapy-related toxicities to baseline or grade ≤ 1 and/or from whom ≥ 25% of the bone marrow has been previously irradiated. 5. Major surgery (defined as requiring general anesthesia)

	or significant traumatic injury within 28 days of start of study drug, or patients who have not recovered from the side effects of any major surgery. 6. Grade ≥ 2 peripheral neuropathy. 7. Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia. 8. History of type I or type II diabetes mellitus either requiring insulin or with a baseline fasting glucose > 150 mg/dL (8.3 mmol/L) or high hemoglobin A1c (HbA1c) as defined as > 7%. Patients who are on a stable dose of oral diabetes medication during at least two weeks prior to initiation of study treatment are eligible for enrolment. 9. Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia). 10. History of malabsorption syndrome or other condition that would interfere with enteral absorption or results

	in the inability or unwillingness to swallow pills. 11. History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis). 12. Known hypersensitivity reaction to any investigational or therapeutic compound or their incorporated substances. 13. Patients have a concurrent malignancy or malignancy within five years of study enrollment with the exception of carcinoma in situ of the cervix, non-melanoma skin carcinoma, or stage I uterine cancer. For other cancers considered to have a low risk of recurrence, discussion with the Medical Monitor is required. 14. Current known infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV). Patients with past HBV infection or resolved HBV infection (defined as having a negative hepatitis B surface antibody [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. 15. Active uncontrolled infection at the time of enrollment. 16. Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) > 480 milliseconds. 17. Patients have an active cardiac disease or a history of cardiac dysfunction including any of the following: a) Unstable angina pectoris or documented myocardial infarction within six months prior to study entry. b) Symptomatic pericarditis. c) Documented congestive heart failure (New York Heart Association functional classification III- IV). d) Left ventricular ejection fraction (LVEF) < 50% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO).

	18. Patients have any of the following cardiac conduction abnormalities: a) Ventricular arrhythmias except for benign premature ventricular contractions. b) Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication. c) Conduction abnormality requiring a pacemaker. d) Other cardiac arrhythmia not controlled with medication. 19. Patients have any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment contraindicate patient participation in the clinical study. 20. Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 14 days or five drug-elimination half-lives, whichever is longer, prior to initiation of study treatment. 21. Pregnant, breastfeeding, or intending to become pregnant during the study or within 28 days after the last

	dose of ipatasertib (GDC-0068), three months after the last dose of eribulin, and six months after the last dose of carboplatin and gemcitabine or capecitabine, whichever occurs later. 22. Treatment with approved or investigational cancer therapy within 14 days prior to initiation of study drug. 23. Concurrent participation in other interventional clinical trial.
Treatment	After signing ICF and confirmed eligibility, patients will be assigned to one of the following three treatment arms based on local investigator assessment and slots availability and will be enrolled in groups of 3: • **Arm A**: Ipatasertib (GDC-0068) 400 milligrams (mg) tablets administered orally once a day (noon) on Days 1-14 of each 21-day cycle plus capecitabine 1000 mg/m^2 tablets orally twice a day (morning and evening; equivalent to 2000 mg/m^2 total daily dose), for 14 days (followed by a 7-day rest period) every 21-day cycle. • **Arm B**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day on Days 1-14 of each 21-

	day cycle plus eribulin 1.23 mg/m^2 (equivalent to eribulin mesylate at 1.4 mg/m^2) administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle. • **Arm C**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus carboplatin AUC5 on Day 1 administered intravenously plus gemcitabine 1000 mg/m^2 administered intravenously over 30 minutes on Days 1 and 8, every 21-day cycle. We expected to recruit 18 patients in each arm. However, patients could be assigned to one of the other open treatments if one arm was stopped due to feasibility or safety reasons. At the end of the study all 54 patients will be recruited, unless all arms were discontinued. Prophylactic loperamide is recommended for all patients during at least the first initial cycle of treatment and may be extended to the next cycle if necessary. A run-in phase for safety and tolerability of ipatasertib (GDC-0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine will

	be conducted as an initial step of the non-comparative phase IIa study where the subjects will be assigned in groups of 3. Patients will be followed to observe if they experience any significant toxicity during the two first cycles. Patients will receive treatment until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment for any other reason. Patients who develop isolated progression in the brain can continue with study treatment at the discretion of the investigator as long as that is considered to be in the best interest of the patient and no new anticancer treatment is initiated. Patients discontinuing the study treatment period will enter a post-treatment follow-up period during which survival and new anti-cancer therapy information will be collected every three months (± 14 days) from the last dose of study treatment up to the end of study (EoS).
Efficacy and safety assessments	**Patient visits**: Visits are organized in programmed cycles of 21 days (if there are no delays in treatment owing to the occurrence of an AE). All visits must occur within ± 2 working days (± 1 working day in Day 8 of each cycle) from the

	scheduled date, unless otherwise noted in the schedule of assessments. Assessments scheduled for Days 1 and 8 of each cycle must be performed within 48 hours and 24 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up. **Tumor assessments:** CT of the chest, abdomen, and pelvis or MRI of the abdomen and pelvis with a non-contrast CT scan of the chest, in patients for whom CT scans with contrast are contraindicated, will be performed every six weeks (± 3 days) from the first dose of study treatment for the first six months and, thereafter, every nine weeks (± 7 days) until the EoS. Imaging should continue to be performed until radiologic evidence of disease progression, treatment discontinuation, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. For estimation of PFS, TTR, ORR, DoR, CBR, OS, and best percentage of change in target tumor lesions, tumor assessment will be based on RECIST v.1.1.

	Patients who discontinue treatment without evidence of disease progression per RECIST v.1.1, in addition to post-treatment follow-up, will be followed every nine weeks (± 7 days) for tumor assessments until documented progression per RECIST v.1.1, elective withdrawal from the study, the start of new anti-cancer treatment, or study completion or termination. Bone scans are mandatory at baseline for all patients and thereafter will be repeated every 24 weeks (± 7 days) only for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression. Brain imaging (MRI) during the trial should be performed in subjects with known brain metastases prior to study initiation (every six weeks [± 3 days] for first six months, then every nine weeks [± 7 days]), and those with worsening and/or new neurological symptoms. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the

	required disease assessments will result in the inability to determine disease status for that time point. **Safety assessments:** The occurrence and maximum grade of side effects observed throughout the study will be listed and tabulated according to type and dose level. Any AEs that the investigator reports as unrelated to the drug will also be reported. In this study, side effects will be assessed according to the NCI-CTCAE v.5.0.
Translational studies	**Tumor samples for molecular analysis:** Patients must agree to provide a tumor tissue sample from a metastatic site or the primary breast tumor at the time of study entry, with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived metastatic tumor specimen only upon agreement from the Sponsor. If feasible, patients will also be given the option of providing a tumor tissue sample at disease progression from metastasis or primary breast tumor.

	Blood samples for molecular analysis: These samples will be collected during the screening period, after two cycles of study treatment, and upon progression or study termination.
Statistics	Sample size: A total sample of 54 evaluable taxane-pretreated patients (safety run-in + non-comparative phase) with unresectable locally advanced or metastatic TNBC will be allocated based on investigator's criteria, in accordance to previous patient's treatments and slots availability, to one of the following treatment arms: • Arm A: Ipatasertib (GDC-0068) plus capecitabine. • Arm B: Ipatasertib (GDC-0068) plus eribulin. • Arm C: Ipatasertib (GDC-0068) and carboplatin plus gemcitabine. We expected to recruit 18 patients in each arm. However, patients could be assigned to one of the other open treatments if one arm was stopped due to feasibility or safety reasons. At the end of the study all 54 patients will be recruited, unless all arms were discontinued. Justification of sample size: This is a pilot study to determine the safety and tolerability of three

	different study combinations with non-taxane chemotherapy agents and ipatasertib (GDC-0068). The analysis will be exploratory without hypothesis testing. However, the Sponsor has estimated the precision for the incidence of adverse events rate in ipatasertib combinations. Based on LOTUS Clinical Trial, the Sponsor assumes a 100% incidence of all grades and 50% grade≥3 adverse events, respectively.
Study periods	**Study follow-up period:** Patients discontinuing the study treatment will enter a post-treatment follow-up period during which survival and new anti-cancer therapy information will be collected every three months (± 14 days) from the last dose of study treatment up to the EoS. **EoS:** EoS is defined as the last patient's last visit at the end of the follow-up period. This will be the last data collection point, which can be a clinic visit or a laboratory sample. EoS will occur at 12 months after the last patient included in the study, unless premature termination of the study.

2 BACKGROUND AND STUDY RATIONALE

2.1 Breast Cancer Molecular Subtypes

Breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer death in women (1). Breast cancer alone is expected to account for 30% of all new cancer diagnoses in women. According the Kantar Health CancerMPact® database, the prevalence of breast cancer range between 41 and 73 per 100,000 population across Europe, and the prevalence of metastatic breast cancer is of 8% in United Kingdom and Italy, and 10% in Germany, France, and Spain.

Breast cancer is a heterogeneous disease with multiple clinical presentations and tumor characteristics. Gene expression profiling studies have classified breast tumors into a number of distinct biological and intrinsic subtypes with prognostic and therapeutic implications, thus providing a new molecular classification of breast cancer (2).

According to this classification, five different molecular subtypes have been identified: luminal A, luminal B, Human Epidermal Growth Factor Receptor 2 (HER2)-enriched, normal breast-like, and basal-like (BL). In contrast to BL tumors, which do not express estrogen receptor (ER), progesterone receptor (PgR), and ER-related genes, luminal tumors express luminal cytokeratins and have the highest levels of ER expression. On the other hand, HER2-enriched tumors overexpress HER2-associated genes but do not express genes that define the luminal subtype (3). BL and HER2-enriched breast cancers have poor outcomes, and among ER-positive subtypes, luminal B tumors have a significantly worse prognosis than luminal A (4).

This understanding of the molecular biology of breast cancer have increased the treatment options of this complex disease, resulting in significant improvements in patient outcomes and a more personalized therapy. For this reason, it is very important for physicians to distinguish between these molecular subtypes in the clinical practice. Although the best way to perform breast tumor intrinsic subtyping is to use microarrays for gene expression analysis, molecular profiling is not ready for use in clinical decision making. Therefore, a combination of immunohistochemical surrogate markers, using ER and PgR status, HER2 status, histological grade, and Ki67 levels, has been validated for molecular subtyping (4,5).

2.2 Triple-Negative Breast Cancer (TNBC)

TNBC accounts for approximately 10%–15% of all diagnosed breast cancers. The majority of these tumors do not usually express hormone receptors (ER and PgR) and HER2, and this is why they are also known as TNBC. However, while most BL tumors are triple-negative and most TNBCs are BL, not all TNBCs are BL and not all BL tumors are triple-negative (6).

TNBC has a worse prognosis than other tumor subtypes. This may result from its aggressive tumor biology, or rather it may be because this tumor subtype does not respond to either hormonal or anti-HER2 therapy. In consequence, these tumors are more likely to have high histological grade and usually present a peak risk of recurrence during the first three years, with a rapid progression from distant recurrence to death, and with the majority of deaths occurring within the first five years after diagnosis (7).

TNBC shows an exceptional chemosensitivity. It has been demonstrated that patients with TNBC have increased rates of pathological complete response (pCR) after neoadjuvant systemic therapy compared to luminal tumors, and those patients who achieved pCR, have an excellent survival. However, patients with residual disease after neoadjuvant systemic therapy have a worse prognosis (8). This different chemosensitivity reflects a clear heterogeneity within this tumor subtype. Regarding this issue, a new intrinsic subtype has been recently recognized (9). The tumors in this subtype, referred to as claudin-low, tend to be TNBC but are enriched with markers linked to epithelial-to-mesenchymal transition and stem cell function, and therefore show a lower rate of pCR after neoadjuvant chemotherapy compared to BL tumors (10).

In an attempt to better identify BL tumors in the daily practice, an expanded surrogate immunopanel of ER, PgR, HER2, Epidermal Growth Factor Receptor (EGFR), and CK5/6 has been proposed (11). Among triple-negative patients, the additional expression of EGFR and/or CK5/6 may identify a subgroup of patients with significantly worse outcome, providing a more specific definition of BL breast cancer.

2.3 TNBC Subtypes

Molecular profiling using cluster analysis from 21 breast cancer data sets identified six different TNBC subtypes characterized by unique gene expression profile and ontologies, including two BL (BL1 and BL2), mesenchymal, mesenchymal stem-like (MSL), immunomodulatory, and luminal androgen receptor (LAR)-enriched tumors (12). The BL subtypes represented BL-breast cancer (BLBC)-like phenotypes, with expression of genes involved in cell cycle and deoxyribonucleic acid (DNA) damage repair in the BL1 subtype, and growth factor signaling pathways in the BL2 subtype. The two mesenchymal-related subtypes were closely associated with epithelial-mesenchymal transition and relative chemo-resistance. Immune-related signatures were abundantly found in the immunomodulatory subtype, whereas the LAR subtype highly expressed androgen receptor and a luminal-like gene expression signature.

Interestingly, a correlative analysis comparing Lehmann's classifications and the PAM50 subtypes classified the majority of TNBC subtypes as BLBC, MSL, and LAR (13). Furthermore, previous sub-classification of TNBC have been revised to a more concise system and consisting of only four subtypes: BL1, BL2, mesenchymal, and LAR (14).

On the other hand, a new classification was recently proposed based on the hypothesis of a possible intersection between immunological and metabolic signatures in tumor microenvironment. Adams and colleagues suggested a subtype with enriched tumor-infiltrating lymphocytes (TILs) and programmed death ligand 1 (PD-L1) expression and activated glycolytic pathways, that have prognostic significance and implications for therapies targeting immune checkpoints and tumor metabolism (15).

However, apart from few retrospective studies suggesting the potential predictive role of certain molecular subtypes in patients treated with neoadjuvant chemotherapy (14,16), it still remains unclear whether the molecular classification itself could be a firm predictive biomarker for patients with TNBC.

2.4 Current Treatment Options in Metastatic TNBC

Compared with luminal breast cancers, TNBC is associated with an aggressive natural history and poor clinical outcomes. In a retrospective analysis, TNBC compared with other women with breast cancer had an increased likelihood of distant recurrence (hazard ratio [HR] 2.6; 95% confidence interval [CI] 2.0-3.5; p<0.0001) and death (HR 3.2; 95% CI 2.3-4.5; p<0.001) within five years of diagnosis (7).

Chemotherapy remains the mainstay of treatment for TNBC with disappointing results because despite the high sensitivity of early-stage TNBC to cytotoxic agents, this treatment is associated in the metastatic setting with relatively low rates of antitumor response ranging from 10% to 30% along with a short median progression-free survival (PFS) that range from around six months in the first-line setting to approximately three months in refractory patients (17–19).

Thus, numerous efforts are currently being undertaken to develop more effective therapeutic strategies in order to improve the overall outcome of TNBC patients, and new advances in the knowledge of molecular biology of TNBC are increasing the treatment options of this complex disease.

2.4.1 Antiangiogenics

Angiogenesis plays an important role in cancer progression. Development of new vessels is decisive for the growth and spread of tumor cells, because malignant tumors are unable to grow beyond a few millimeters without new vasculature (20). In breast cancer, several studies have found an inverse correlation between overall survival (OS) and Vascular-Endothelial Growth Factor (VEGF) expression (21,22). Linderholm and colleagues analyzed the relationship between intratumoral VEGF levels and OS in patients with TNBC and non-TNBC. Compared with non-TNBC, patients with TNBC had significantly higher VEGF levels and worse survival (23). In

addition, increased VEGF expression predicts poor response to systemic therapy with tamoxifen and chemotherapy (24). For these reasons, a large number of antiangiogenic agents are being tested in patients with breast cancer, and more specifically in TNBC.

Bevacizumab is a humanized monoclonal antibody that can recognize all known isoforms of VEGF-A and prevents receptor binding, thereby inhibiting angiogenesis and tumor growth. The most common side effects of this agent include hypertension, proteinuria, and headache. As a single-agent, bevacizumab has shown modest activity in patients with metastatic breast cancer. However, better results have been reported in combination with chemotherapy. To date, five phase III clinical trials have evaluated the addition of bevacizumab to chemotherapy in the first- and second-line treatment of patients with metastatic breast cancer. In the first-line setting, three studies have been performed: Eastern European Cooperative Oncology Group (ECOG) 2100 (25); AVADO (26); and RIBBON 1 (27). In the second-line setting, the results of two studies have been reported: AVF2119g (28) and RIBBON 2 (29,30). PFS was the primary objective of all these studies.

A meta-analysis from three randomized trials of bevacizumab and first-line chemotherapy showed that the addition of bevacizumab resulted in statistically significant improvements in PFS, the primary endpoint of these studies, and objective response rate (ORR). Subgroup analysis demonstrated that TNBC patients achieved a similar benefit from bevacizumab as did non-TNBC patients (HR for PFS: TNBC 0.63; non-TNBC 0.64) (31). In the second-line setting, subgroup analysis from RIBBON2 trial revealed that the benefit of the combination seems to be greater in patients with TNBC compared to hormone receptor-positive tumors (HR for PFS: TNBC 0.53; non-TNBC 0.89) (32).

Finally, the IMELDA randomized phase III study included 284 patients with HER2-negative metastatic breast cancer that had received bevacizumab plus docetaxel as first-line therapy (33). A total of 185 patients with complete response (CR) or partial response (PR), or stable disease (SD), were randomized to receive bevacizumab with or without capecitabine as maintenance therapy. The primary endpoint was PFS (from randomization) in the intention-to-treat population. The rationale of this study was based on the cumulative toxic effects of prolonged exposure to taxane-based chemotherapy and the association of longer first-line chemotherapy duration with better OS and PFS. Despite prematurely terminated accrual, sequential maintenance treatment with capecitabine plus bevacizumab showed significantly longer median PFS (11.9 vs. 4.3 months, HR 0.38, 95% CI 0.27-0.55, p<0.0001) and median OS (39.0 vs. 23.7 months, HR 0.43, 95% CI 0.26-0.69, p=0.0003) than monotherapy with bevacizumab while maintaining the quality of life. In a subgroup analysis, the combination of bevacizumab and capecitabine specially favored those patients with visceral metastases or with three or more metastatic organ sites. The benefit of adding capecitabine was irrespective of hormone receptor status.

The IMELDA strategy combines the efficacy of bevacizumab and the benefit of maintenance chemotherapy and represents an excellent therapeutic option for the first-line treatment of patients with metastatic TNBC.

2.4.2 Poly(ADP-Ribose)Polymerase (PARP) Inhibitors

Immunohistochemical profile of BL tumors is similar to those tumors arising in *Breast Cancer 1* (*BRCA1)* mutation carriers, and subsequently the majority of these inherited tumors have a BL phenotype. Likewise, dysfunction of the BRCA1 pathway caused by *BRCA1* gene promoter methylation is also a frequent event in sporadic BL tumors.

PARP1 and PARP2 play a fundamental role in repairing single-strand breaks through the base excision repair mechanism. However, in carriers of germline *BRCA* mutations, the simultaneous inhibition of a compensatory repair mechanism PARP-dependent will induce cell death either through mitotic catastrophe or apoptosis (synthetic lethality).

There are a number of PARP inhibitors under clinical evaluation. Talazoparib inhibits PARP with an efficacy comparable to olaparib and rucaparib but is approximately 100-fold more potent in trapping PARP-DNA complexes leading to a higher cytotoxicity.

The randomized phase III OlympiAD trial provided a significant benefit of olaparib over single-agent standard therapy (capecitabine, vinorelbine, or eribulin). A total of 302 patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation were included. Median PFS, the primary endpoint of the study, was longer in the olaparib group than in the standard-therapy group (7.0 vs. 4.2 months; HR 0.58; 95% CI 0.43-0.80; p<0.001) (34).

Efficacy of talazoparib was also confirmed in the randomized phase III EMBRACA trial. In this study, talazoparib was compared with standard single-agent therapy of the physician's choice (capecitabine, eribulin, gemcitabine, or vinorelbine) in 431 patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation. Median PFS, the primary endpoint of the study, was longer in the talazoparib group than in the standard-therapy group (8.6 vs. 5.6 months; HR 0.54; 95% CI 0.41-0.71; p<0.001). Furthermore, significant overall improvement in quality of life was observed in talazoparib (35).

Based on these results, PARP inhibitors represent a new effective option for women with *BRCA*-mutated, HER2-negative metastatic breast cancer.

2.4.3 Immunotherapy

Multiple lines of preclinical and clinical evidence have demonstrated that tumors can evade destruction by the immune system by expressing surface ligands that engage inhibitory receptors on tumor-specific T cells and induce immune tolerance. Immune-related signatures have been abundantly found within TNBC, more specifically in the immunomodulatory subtype.

Early results of immunotherapy with immune checkpoint inhibitors in patients with metastatic TNBC have demonstrated encouraging activity with durable responses and substantial OS in pre-treated patients. Unfortunately, there is a relatively small subset of patients that derive a benefit from single-agent treatment. However, the increasing evidence in other cancers that combination with chemotherapy could improve the anti-tumor activity of PD-L1-targeted therapy led to the evaluation of the combination of chemotherapy and immunotherapy in patients with metastatic TNBC with striking results.

The recently completed randomized phase III IMpassion130 trial enrolled a total of 902 patients with untreated metastatic TNBC who were randomized to nab-paclitaxel plus atezolizumab or nab-paclitaxel plus placebo (36). Stratification factors were the use of (neo)adjuvant taxane therapy (yes vs. no), the presence or absence of liver metastases at baseline, and PD-L1 expression at baseline (positive vs. negative).

The two primary endpoints of the study were PFS, in the intention-to-treat (ITT) population and PD-L1–positive subgroup, and OS (tested in the ITT population; if the finding was significant, then it would be tested in the PD-L1–positive subgroup).

The addition of atezolizumab significantly increased median PFS in the ITT analysis (7.2 vs. 5.5 months; HR 0.80; 95% CI 0.69-0.92; p=0.002) and among patients with PD-L1–positive tumors (7.5 vs. 5.0 months, HR 0.62; 95% CI 0.49-0.78; p<0.001).

In the ITT analysis, median OS was 21.3 months with atezolizumab plus nab-paclitaxel and 17.6 months with placebo plus nab-paclitaxel (HR 0.84; 95% CI 0.69-1.02; p=0.08); among patients with PD-L1–positive tumors, median OS was 25.0 months and 15.5 months, respectively (HR 0.62; 95% CI 0.45-0.86).

This study will probably change the treatment landscape of metastatic TNBC patients, and this combination should become a new treatment option in the first-line setting for patients with PD-L1 positive metastatic TNBC.

2.4.4 Antibody Drug Conjugates

Integrating the tumor specificity provided by unique monoclonal antibodies and cytotoxicity of small molecule drugs, antibody-drug conjugates are a series of smart chemotherapeutics that have recently shown great promise in treating a number of cancer types. Antibody drug

conjugates are designed to selectively attack and kill cancer cells with minimal toxicity to normal tissues.

New antibody-drug conjugates such as sacituzumab govitecan (IMMU-132), glematumumab vedotin, and SGN-LIV1A have demonstrated important antitumor activity in metastatic TNBC and are currently evaluated in this population. Sacituzumab govitecan (IMMU-132) is being already assessed into a phase III trial for patients with heavily-pretreated metastatic TNBC (NCT02574455), considering the promising results of this agent in a single-arm phase II study (37).

Sacituzumab govitecan (IMMU-132) is an antibody drug conjugate that binds to Trop-2 for targeted delivery of SN-38 (active metabolite of irinotecan) directly to the tumor cell while minimizing systemic exposure of SN-38 to decrease host toxicity. Trop-2 antigen is highly expressed in TNBC. For this reason, this drug was evaluated as a third-line and beyond therapy option in a single-arm phase II study of 110 patients with metastatic TNBC, demonstrating a significant clinical activity as a single-agent in this population (38). ORR was 34% with a median duration of response (DoR) of 7.6 months (95% CI 4.8-11.3) and a clinical benefit rate (CBR) of 46%. Median PFS was 5.5 months (95% CI 4.8-6.6) and median OS was 12.7 months (95% CI 10.8-13.6). IMMU-132 showed an acceptable toxicity profile with nausea, alopecia, neutropenia, and diarrhea being the most common and relevant toxicities.

2.4.5 Antiandrogens

LAR subtype is characterized by androgen receptor signaling with a gene expression pattern similar to luminal breast cancer. Patients with LAR tumors are more slowly growing when metastatic, however they have decreased relapse-free survival in the adjuvant setting relative to other TNBC subtypes, perhaps due to lower chemotherapy sensitivity. LAR cell line models are sensitive to the androgen receptor partial antagonist bicalutamide and are even more sensitive to the next-generation androgen receptor inhibitor enzalutamide.

AR is expressed in 12–55% of cases of TNBC, because although the LAR subtype is enriched for expression of the androgen receptor an its gene targets, other TNBC subtypes also express androgen receptor. However, some of the variability in frequency of expression between studies is due to diverse immunohistochemistry (IHC) assays used and to different assay cutoffs (1 vs. 10%). Optimal IHC assay and cutoff for response to androgen receptor inhibitors in clinic remains unknown (39).

Early results from two clinical phase II studies with single-agent anti-androgens have confirmed a promising antitumor activity in patients with metastatic TNBC. First, the efficacy of bicalutamide was assessed in 26 patients with metastatic androgen receptor-positive (immunohistochemistry [IHC] ≥ 10%) TNBC demonstrated a CBR at 24 weeks of 19% with a median PFS of 12 weeks

(95% CI 11-22) (40). More recently, enzalutamide has been also evaluated in 118 metastatic TNBC patients with ≥ 1% of androgen receptor assessed by IHC (41). In this study, CBR at 16 and 24 weeks were 25% and 20%, respectively. In patients with ≥ 10% of androgen receptor expression (N = 75), CBR at 16 and 24 weeks were 35% and 29%, respectively, with 8% of patients achieving a CR or PR. Median PFS was 14.7 weeks (95% CI 8.1-19.3). Interestingly, a proprietary androgen-driven gene signature called PREDICT AR was created from gene expression profiling, and patients whose tumors were positive for this signature had increased PFS compared to those without an androgen-driven gene signature (32 vs. 9 weeks) (42).

2.5 Relevance of the PI3K-AKT-mTOR signaling pathway

The serine/threonine kinase B (AKT) is encoded by three closely related genes in mammals, *AKT1*, *AKT2*, and *AKT3*. AKT is the central node of the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway, in which activation is associated with proliferation, cell cycle progression, and survival. The direct product of PI3K activity, the lipid second messenger, phosphatidylinositol (3,4,5)-trisphosphate (PIP3), promotes membrane association of AKT. AKT is phosphorylated at two critical residues for its full activation: a threonine residue in the activation loop of the kinase domain (threonine 308 in AKT1) by phosphoinositide-dependent kinase 1 (PDK1) and a serine residue within the hydrophobic motif of the regulatory domain (serine 473 in AKT1) by mTOR Complex 2 (mTORC2) (43). In turn, activated AKT phosphorylates and regulates the functions of numerous cellular proteins, including FOXO, mTORC1, and S6 kinase (44).

Negative regulation of the PI3K-AKT-mTOR pathway occurs through several mechanisms, and at the level of AKT, phospholipid phosphates and protein phosphatases are central regulators. The tumor suppressor phosphatase and tensin homolog (PTEN), a phospholipid phosphatase, dephosphorylates PIP3, limiting AKT translocation and activation at the cell membrane.

Additionally, protein phosphates, including protein phosphatase 2A and PH domain and leucine-rich repeat protein phosphatases, dephosphorylate the serine and threonine residues that are required for the kinase activity of AKT.

The PI3K-AKT-mTOR pathway is activated by numerous genetic and non-genetic mechanisms across the spectrum of cancer (45). The most commonly found alterations in this pathway result from decreased expression or inactivating mutations of PTEN, activating mutations of p110α catalytic subunit of PI3K (*PIK3CA*), deregulation of receptor tyrosine kinase signaling, and amplification or activating mutations of receptor tyrosine kinases. In addition, alterations in AKT itself, including amplification and overexpression of individual AKT isoforms, as well as activating mutations in *AKT*, most commonly an E17K mutation in the PH domain of AKT1 that results in PI3K-independent membrane recruitment of AKT1, have been identified in a subset of human cancers (46,47).

Hyperactivation of AKT also occurs via deregulated signaling of many cell surface receptors and intracellular linkers and signaling molecules, and amplification/mutation of the EGFR/ErbB growth factor receptor family members (47). Moreover, AKT activation has been associated with resistance to both chemotherapeutic agents and targeted agents such as trastuzumab and tamoxifen (48,49).

Besides being an important driver of cell proliferation, growth, and survival, all of which are involved in tumorigenesis, AKT also plays a key role in glucose homeostasis and mediates the metabolic effects of insulin downstream of the insulin receptor (a receptor tyrosine kinase) (50,51).

In summary, AKT is a central node in cell signaling downstream of growth factors, cytokines, and other cellular stimuli. It plays an important role in cancer development, progression, and therapeutic resistance and is activated in most, if not all, human cancers (52). The ubiquity and importance of AKT activation in human cancers provide a strong rationale for developing therapeutics targeting AKT.

2.6 PI3K/AKT Pathway in Breast Cancer

In breast cancer, the PI3K-AKT-mTOR pathway is more frequently activated by genomic aberrations than any other signaling pathway (45). The most common genetic alterations in this pathway are activating mutations of *PIK3CA*, loss-of-function alterations of the tumor suppressor *PTEN*, deregulation of receptor tyrosine kinase signaling, and amplification and mutations of receptor tyrosine kinases (53,54). 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 (46–48). 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 (44).

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 (53). 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 luminal breast cancers (53).

To date, the relationship between PI3K/AKT pathway activation and prognosis in 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 (55). 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 (54).

2.7 Ipatasertib (GDC-0068)

Ipatasertib (GDC-0068) is a potent and selective small-molecule inhibitor of all three isoforms of the serine/threonine kinase AKT. Ipatasertib (GDC-0068) selectively binds to the active conformation of AKT and inhibits its kinase activity (56). Consistent with its mechanism of action in nonclinical studies, ipatasertib (GDC-0068) has proven to be especially effective on cells with activated AKT, including *PTEN*-null and *PI3K*-mutated tumor models, leading to suppression of the phosphorylation of its direct substrates. Consistent with the role of AKT in insulin signaling, ipatasertib (GDC-0068) also exhibited dose-dependent and reversible elevation of serum glucose in nonclinical studies. *In vivo* activity studies support the use of ipatasertib (GDC-0068) as a single-agent or in combination with chemotherapeutic, hormonal, or targeted agents for the treatment of patients with advanced or metastatic solid tumors (57).

2.7.1 Overview of Clinical Development

Ipatasertib (GDC-0068) is being developed by Genentech/Roche as a single-agent and in combination with other therapies for the treatment of cancers in which activation of the PI3K-AKT-mTOR pathway may be relevant for tumor growth or therapeutic resistance.

As of 30 June 2018, the first-in-human phase I dose-escalation study in patients with advanced solid tumors has been completed and it determined the safety profile and the maximum tolerated dose (MTD) for single-agent ipatasertib (GDC-0068). Interim analysis has been completed for the Phase Ib dose-escalation Study PAM4983g (NCT01362374) in patients with advanced solid tumors. This study determined the safety profile, pharmacokinetic (PK) interactions of ipatasertib (GDC-0068) in combination with other anticancer agents, and the recommended phase II dose (RP2D) for ipatasertib (GDC-0068) in each combination.

Primary analyses have been also completed for two randomized phase II studies to evaluate the safety and efficacy of ipatasertib (GDC-0068) in combination with paclitaxel in patients with locally advanced or metastatic TNBC (Study GO29227; NCT02162719) and in patients with early TNBC (Study GO29505; NCT02301988).

Additional phase Ib and phase III trials have been initiated in patients with breast cancer (Studies CO40115; NCT03424005), (CO40016; NCT03337724), (CO39611; NCT03280563), and (CO40151; NCT03800836) and enrollment is ongoing.

Further clinical development of ipatasertib (GDC-0068) will be based on identifying tolerable dosing regimens that provide adequate exposure as well as evidence of pharmacodynamic and/or clinical activity, either as a single-agent or in combination with other anticancer therapies. In addition, the predictive effect of biomarkers will be further evaluated in future studies in prostate cancer, breast cancer, and other malignancies with high prevalence of PI3K-AKT pathway alteration.

2.7.2 Clinical Efficacy

2.7.2.1 Single-Agent Ipatasertib (GDC-0068)

- **Study PAM4743g**

In the phase I clinical study of ipatasertib (GDC-0068), Study PAM4743g (NCT01362374) anti-tumor activity in patients was evaluated by radiographic responses using RECIST v.1.0 guidelines. Exploratory FDG-PET assessments were also evaluated in a cohort of patients with breast cancer with PI3K-AKT-mTOR pathway-activated tumors (58).

As of 2 February 2015, a total of 30 patients were enrolled in Stage 1 (dose-escalation phase); 16 and six patients were enrolled in Stage 2 and 3 (expansion phases), respectively. Post-treatment tumor assessment data are available for 47 of the 52 enrolled patients.

Overall, for the 47 patients for whom response data were available across all doses of the phase I study, 16 patients (34.0%) achieved SD or incomplete response as a best response per RECIST v.1.0 as assessed by the investigators, including 11 of 25 patients (44.0%) treated at the maximum tolerated dose (MTD) of 600 milligrams (mg) daily. PFS greater than six months was observed in six patients with breast (N = 2), chondrosarcoma (N = 1), colorectal (N = 1), lung (N = 1), and prostate cancer (N = 1). No PR or CR were observed.

In Stage 2 of this phase I study, patients with metastatic castration resistant prostate cancer (mCRPC) (N = 5) or diagnostic positive (tumors with activated PI3K-AKT pathway) breast cancers (N = 10) were enrolled and received ipatasertib (GDC-0068) at the 600 mg dose. Twelve patients (eight with breast cancer and four with mCRPC) had tumor assessments: five of the eight patients (62.5%) with breast cancer, and three of the four patients (75%) with mCRPC achieved SD or incomplete response as assessed by the investigator.

Of the 47 patients for whom post-treatment tumor assessment was available, 41 patients had known tumor molecular status of archival tumor tissues; radiographic SD as best response was observed in six of the nine patients (67%) who had complete loss of PTEN expression, *PIK3CA*, or *AKT1* mutations in their tumor, whereas three patients (33%) had progressive disease (PD) as best response. For patients without alterations, 10 of the 32 patients (31%) had SD, and 22 (69%) had PD as best response.

Radiographic SD was not observed in patients who had known *KRAS* mutations (G12V/D/A or Q61L, N = 7).

2.7.2.2 Ipatasertib (GDC-0068) In Combination with Other Anticancer Agents

- **Study PAM4983g**

Preliminary efficacy data (as of interim analysis cutoff date 02 May 2016) are available from the ongoing Phase Ib Study PAM4983g with ipatasertib (GDC-0068) combined with docetaxel in Arm A, mFOLFOX6 in Arm B, paclitaxel in Arm C, or enzalutamide in Arm D (58).

Across all treatment arms, eight of 101 efficacy-evaluable patients (8%) had a confirmed PR to study treatment (e.g., two confirmed PR in each arm) including the following: two patients in Arm A (7%) with TNBC (N = 1) and esophageal cancer (N = 1); two patients in Arm B (6%) with colorectal cancer (CRC) (N = 1) and esophageal cancer (N = 1); two patients in Arm C (7%) with luminal breast cancer (N = 2); and two patients in Arm D (11.8% of patients with measurable disease) with mCRPC (N = 2). Of the eight patients who had confirmed PRs, six patients remained progression-free for more than six months, including patients who had prior exposure to the same chemotherapy or abiraterone/enzalutamide treatment or investigational PI3Kalpha inhibitors.

In patients who had measurable disease and known molecular status of archival tumor tissues in Arms A, B, C, and D, confirmed response rates by RECIST v.1.1 are summarized by *PIK3CA/AKT1* mutation status (***Table 1***). Four of 14 patients (28.6%) with known *PIK3CA/AKT1* activating mutation in their tumor archival tissues had a PR, versus two of 46 patients (4.3%) with no detectable *PIK3CA/AKT1* mutations.

Table 1. RECIST Response Outcomes for Patients with Baseline Measurable Disease by Mutation Status.

	Arm A (N = 26 TNBC patients)	**Arm B** (N = 33 CRC/Esophageal patients)	**Arm C** (N = 25 ER+/HER2- patients)	**Arm D** (N = 17 mCRPC patients)
***AKT1/PIK3CA* Activating Mutation**				
Best Response				
CR	0	0	0	0
PR	1 (3.8%)	1 (3.0%)	2 (8.0%)	0
SD	1 (3.8%)	3 (9.1%)	4 (16%)	0
PD	1 (3.8%)	0	0	0
Not evaluated	1 (3.8%)	0	0	0
***AKT1/PIK3CA* Non-Altered**				
CR	0	0	0	0
PR	1 (3.8%)	1 (3.0%)	0	0
SD	9 (34.6%)	10 (30.3%)	5 (20%)	0
PD	3 (11.5%)	7 (21.2%)	2 (8.0%	0
Not evaluated	1 (3.8%)	3 (9.1%)	3 (12%)	1 (5.9%)
***AKT1/PIK3CA* Unknown**				
CR	0	0	0	0
PR	0	0	0	2 (11.8%)

	Arm A (N = 26 TNBC patients)	**Arm B** (N = 33 CRC/Esophageal patients)	**Arm C** (N = 25 ER+/HER2- patients)	**Arm D** (N = 17 mCRPC patients)
SD	4 (15.4%)	4 (12.1%)	5 (20%)	4 (23.5%)
PD	3 (11.5%)	3 (9.1%)	4 (16%)	7 (41.2%)
Not evaluated	1 (3.8%)	1 (3%)	0	3 (17.6%)
CR=complete response; CRC=colorectal cancer; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; mCRPC= metastatic castration resistant prostate cancer; PD=progressive disease; PR=partial response; SD=stable disease; TNBC=triple-negative breast cancer. Note: Cutoff date 02 May 2016. Note that N indicates the number of efficacy-evaluable patients.				

A total of 16 patients remained progression-free for more than six months. Three of these patients (11% of Arm A) with tumor types of cervix (N = 1) and lung (N = 2) were administered docetaxel and ipatasertib (GDC-0068). Six of these patients (18% of Arm B) with tumor types of appendiceal (N = 1), CRC (N = 3), esophageal (N = 1), and sexual cordons (N = 1) were administered mFOLFOX6 and ipatasertib (GDC-0068). Three of these patients (11% of Arm C) with breast cancer (luminal [N= 2], TNBC [N = 1]) were administered paclitaxel and ipatasertib (GDC-0068). And four of these patients (12% of Arm D) with prostate cancer were administered enzalutamide and ipatasertib (GDC-0068).

- **Study GO29227 (LOTUS)**

This randomized phase II trial investigated the addition of ipatasertib (GDC-0068) to paclitaxel as first-line therapy for inoperable, locally advanced, or metastatic TNBC not amenable to curative treatment (59).

A total of 124 patients were randomized (ratio 1:1) to receive weekly paclitaxel (80 mg/m^2 Days 1, 8, and 15 of a 28-day cycle) with either ipatasertib (GDC-0068) (400 mg Days 1–21 of a 28-day cycle) or placebo. The co-primary endpoints were PFS in ITT population and PFS in the PTEN-low (assessed by a Ventana IHC assay) population. The OS in ITT, PTEN-low and PIK3CA/AKT1/PTEN-altered populations was a prespecified secondary endpoint.

With a median follow-up of 10.4 and 10.2 months in each arm, the addition of ipatasertib (GDC-0068) significantly prolonged median PFS in the ITT population (6.2 versus 4.9 months, HR 0.60, 95% CI 0.37-0.98; p=0.037), but not in the PTEN-low population (38.7%) (6.2 versus 3.7 months, HR 0.59, 95% CI 0.26-0.132; p=0.18) (See ***Table 2***). In the *PIK3CA/AKT/PTEN*-altered tumor population (as assessed by a FoundationOne assay) (33.8%), the addition of ipatasertib (GDC-

0068) achieved a more pronounced effect (9.0 versus 4.9 months, HR 0.44, 95% CI 0.22-0.87; p=0.037).

Final analysis of the LOTUS trial has shown numerically longer overall survival with ipatasertib plus paclitaxel vs placebo plus paclitaxel in the ITT population (25.8 months vs 16.9 months, HR 0.81; 95% CI 0.53-1.23).Similarly, median OS favoured ipatasertib plus paclitaxel vs placebo plus paclitaxel in the PTEN-low (23.1 vs 15.8 months) and PIK3CA/AKT1/PTEN-altered (25.8 vs 22.1 months) subgroups.

Table 2. Overview of PFS Results in Study GO29227.

	Ipatasertib (GDC-0068) plus Paclitaxel	**Placebo plus paclitaxel**
ITT Population		
Number of patients in population	62	62
Number of patients with event (%)	39 (62.9%)	45 (72.6%)
Median duration (months) (90% CI)	6.18 (4.57, 7.33)	4.93 (3.58, 5.36)
Unstratified HR (90% CI)	0.62 (0.43, 0.89)	
Unstratified p-value (Log-Rank test)	0.0266	
Stratified HR (90% CI) (per protocol)	0.60 (0.40, 0.91)	
Stratified p-value (Log-Rank test) (per protocol)	0.0372	
Patients with *PIK3CA/AKT1/PTEN*-altered tumors (determined by FoundationOne NGS assay)		
Number of patients in subpopulation	26	16
Number of patients with event (%	12 (46.2%)	13 (81.3%)
Median duration (months) (90% CI)	9.03 (4.57, 12.88)	4.93 (3.58, 5.39)
Unstratified HR (90% CI)	0.44 (0.22, 0.87)	
Patients with *PIK3CA/AKT1/PTEN* non-altered tumors (determined by FoundationOne NGS assay)		
Number of patients in subpopulation	28	33
Number of patients with event (%)	21 (75.0%)	23 (69.7%)
Median duration (months) (90% CI)	5.32 (3.61, 6.67)	3.65 (2.86, 5.52)
Unstratified HR (90% CI)	0.76 (0.46, 1.27)	

CI=confidence interval; HR=hazard ratio; NGS=next generation sequencing; PIK3CA=PI3K p110alpha isoform; PTEN=phosphatase and tensin homolog.
Note: Clinical cutoff date of 7 June 2016. Percentages are based on the number of patients in the respective (sub)population.

- **Study GO29505 (FAIRLANE)**

This randomized phase II trial investigated the addition of ipatasertib (GDC-0068) to paclitaxel as neoadjuvant therapy for patients with early-stage TNBC (59).

A total of 151 patients were randomized (ratio 1:1) to receive ipatasertib (GDC-0068) (400 mg Days 1–21 of a 28-day cycle) (76 patients) or placebo (75 patients) in combination with paclitaxel (80 mg/m^2 days 1, 8, 15, and 22 of a 28-day cycle). A pCR was reported in a higher proportion of patients in the ipatasertib (GDC-0068) plus paclitaxel arm (17.1%) than in the placebo plus paclitaxel arm (13.3%). The ORR was consistent with other endpoints in a given population of patients with PTEN-low and *PIK3CA/AKT1/PTEN*-altered tumors. In patients with PTEN-low tumors, a 3.3% difference in pCR rate was observed between the ipatasertib (GDC-0068) plus paclitaxel arm (15.8%) and the placebo plus paclitaxel arm (12.5%) (61).

2.7.3 Clinical Safety

- **Study PAM4743g**

Protocol-defined dose-limiting toxicities (DLTs) were reported for two patients (58). Two of the six evaluable patients treated with ipatasertib (GDC-0068) 800 mg daily on Days 1-21 of each 28-day cycle experienced grade 3 asthenia (N = 1) and grade 3 nausea (N = 1), which the investigators assessed as related to ipatasertib (GDC-0068) and which fulfilled the DLT criteria during Cycle 1.

The event of asthenia improved following dose reduction of ipatasertib (GDC-0068), and the event of nausea was managed with anti-emetic medications and resolved while dosing with ipatasertib (GDC-0068) was continued. Therefore, the MTD of single-agent ipatasertib is 600 mg daily on Days 1-21 of each 28-day cycle.

Safety data are available for 51 patients treated with ipatasertib (GDC-0068) in the dose-escalation and expansion stages of Study PAM4743g, including 29 patients treated at a dose of 600 mg. All 51 patients (100%) experienced at least one adverse event (AE) per the US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.3.0.

Forty-seven of 51 patients (92.2%) experienced at least one AE that was assessed by the investigators as related to ipatasertib (GDC-0068). The AEs reported in ≥ 10% of patients that were assessed by the investigators as related to ipatasertib (GDC-0068) were nausea (70.6%), diarrhea (68.6%), vomiting (51.0%), asthenia (37.3%), hyperglycemia (33.3%), decreased

appetite (23.5%), dyspepsia (19.6%), abdominal pain upper (11.8%), dysgeusia (11.8%), and rash (11.8%).

Ten of 51 patients (19.6%) experienced a grade ≥ 3 AE that was assessed by the investigator as related to ipatasertib (GDC-0068); such events reported for two or more patients included asthenia (N = 3) and diarrhea (N = 4). No grade 4 or grade 5 AEs related to ipatasertib (GDC-0068) as assessed by the investigators were reported.

There were five serious adverse events (SAEs) that were assessed by the investigator as related to ipatasertib (GDC-0068): grade 3 asthenia (N = 1, 2.0%), grade 3 diarrhea (N = 1, 2.0%), grade 3 hyperglycemia (N = 1, 2.0%), grade 2 renal failure (N = 1, 2.0%), and grade 3 toxic skin eruption (N = 1, 2.0%).

Three patients experienced SAEs of Grade 5 (malignant neoplasm progression, disease progression, and ischemic stroke), none of which was assessed as related to ipatasertib (GDC-0068) by the investigator.

- **Study PAM4983g**

Common adverse events of ipatasertib (GDC-0068) in combination with docetaxel (Arm A)

Safety data were available for 27 treated patients, including 13 patients with TNBC treated with ipatasertib (GDC-0068) at the MTD dose of 600 mg daily in combination with docetaxel. All 27 patients (100%) experienced at least one AE per NCI-CTCAE v.4.03. No DLTs were observed (58).

Grade ≥ 3 AEs reported at least two patients included neutropenia (N = 5), febrile neutropenia (N = 3), hypophosphatemia (N = 2), and diarrhea (N = 2).

There were six SAEs in four patients that were assessed by the investigator as related to ipatasertib (GDC-0068): Grade 3 hypocalcemia (N = 1, 3.7%), grade 3 hypomagnesemia (N = 1, 3.7%), grade 3 hypophosphatemia (N = 1, 3.7%), grade 3 rash maculopapular (N = 1, 3.7%), grade 2 diarrhea (N = 1, 3.7%), and grade 2 rash (N = 1, 3.7%).

One SAE of grade 5 (septic shock, not related to ipatasertib [GDC-0068] in combination with docetaxel) was reported in Arm A.

Common adverse events of ipatasertib (GDC-0068) in combination with paclitaxel (Arm C)

As of 2 May 2016, safety data were available for 27 treated patients, including 21 patients with luminal breast cancer treated at the RP2D of ipatasertib (GDC-0068) 400 mg daily in combination with paclitaxel.

Twenty-six of 27 patients (96.3%) experienced at least one AE per NCI-CTCAE v.4.03.

One patient treated at 600 mg ipatasertib (GDC-0068) in combination with paclitaxel experienced a grade 3 dehydration DLT (concurrent with grade 3 diarrhea onset), which was assessed by the investigator as related to ipatasertib (GDC-0068), paclitaxel, and illness. Grade 3 dehydration resolved after study drug withdrawal.

Grade ≥ 3 AEs reported in two or more patients included diarrhea (N = 6), hyperglycemia (N = 4), neutropenia (N = 3), anemia (N = 2), pneumonia (N = 2), pyrexia (N = 2), and dehydration (N = 2).

At the RP2D of 400 mg ipatasertib (GDC-0068) daily in combination with paclitaxel, nine of 21 patients (42.9%) experienced grade ≥ 3 AEs, versus five of six patients (83.3%) receiving ipatasertib (GDC-0068) 600 mg daily in combination with paclitaxel.

There were two SAEs that was assessed by the investigator as related to ipatasertib (GDC-0068): Grade 3 diarrhea (N = 1, 3.7%) and grade 3 dehydration (N = 2, 7.4%).

Three grade 5 SAEs (pancreatic carcinoma, mesothelioma, and respiratory failure) were reported from Arm C, none of which was assessed as related to ipatasertib (GDC-0068) in combination with paclitaxel by the investigator.

- **Study GO29227 (LOTUS)**

As of the primary analysis of 7 June 2016, a total of 124 patients with locally advanced or metastatic TNBC were randomized to receive ipatasertib (GDC-0068) at 400 mg on a 21-day on 7-day off schedule or placebo, each in combination with paclitaxel chemotherapy (60,62). One hundred twenty-three patients received at least one dose of study treatment and 61 patients were treated with ipatasertib (GDC-0068).

The number of patients with at least one AE was 61 of 61 patients (100%) and 60 of 62 patients (96.8%) in the ipatasertib (GDC-0068) 400 mg plus paclitaxel arm versus placebo plus paclitaxel arm, respectively.

The most frequent (≥ 5% in any treatment group) AEs of grade ≥ 3 were diarrhea (23.0% vs. 0% in the ipatasertib [GDC-0068] 400 mg plus paclitaxel arm vs. placebo plus paclitaxel arm), neutropenia (9.8% vs. 1.6%), neutrophil count decreased (8.2% vs. 6.5%), and fatigue (3.3% vs. 6.5%).

A total of 27.9% of patients in the ipatasertib (GDC-0068) 400 mg plus paclitaxel arm and 14.5% of patients in the placebo plus paclitaxel arm had experienced at least one SAE.

A total of 11 SAEs across both arms were assessed by the investigator as related to ipatasertib (GDC-0068)/placebo in combination with paclitaxel. Related SAEs reported in more than one patient were diarrhea and febrile neutropenia, both in the ipatasertib (GDC-0068) 400 mg plus paclitaxel arm.

- **Study GO29505 (FAIRLANE)**

A total of 151 patients with early-stage TNBC had been randomized to receive ipatasertib (GDC-0068) (76 patients) or placebo (75 patients) in combination with paclitaxel (61).

Common AEs with an incidence of at least 20% in either treatment arm were diarrhea (ipatasertib [GDC-0068] plus paclitaxel: 86.8% vs. placebo plus paclitaxel: 32.0%), nausea (47.4% vs. 30.7%), constipation (13.2% vs. 21.3%), vomiting (22.4% vs. 5.3%), alopecia (52.6% vs. 53.3%), rash (25.0% vs. 18.7%), asthenia (42.1% vs. 38.7%), fatigue (30.3% vs. 32.0%), dysgeusia (23.7% vs. 22.7%), headache (18.4% vs. 20.0%), and insomnia (19.7% vs. 20.0%).

Diarrhea was the only grade ≥ 3 AE reported in at least 5% of patients in either treatment arm (ipatasertib [GDC-0068] plus paclitaxel: 13 patients [17.1%] vs. placebo plus paclitaxel: One patient [1.3%], all of grade 3) and in at least 3% more patients in the ipatasertib (GDC-0068) plus paclitaxel arm than in the placebo plus paclitaxel arm.

Ipatasertib (GDC-0068)/placebo-related SAEs were GI disorders (ipatasertib [GDC-0068] plus paclitaxel: One patient [1.3%] vs. placebo plus paclitaxel: zero patients), general disorders and administration site conditions (Zero vs. one patient [1.3%]), and metabolism and nutrition disorders (One [1.3%] vs. zero patients). Grade 3 events included diarrhea (one patient in ipatasertib [GDC-0068] plus paclitaxel arm) and dehydration (one patient in ipatasertib [GDC-0068] plus paclitaxel arm).

2.7.4 Potential Drug-Drug Interaction (DDI)

Considering that the below list of medications is not comprehensive, the investigator should consult the prescribing information when determining whether a concomitant medication can be safely administered with study treatment. In addition, the investigator should contact the Medical Monitor if questions arise regarding medications not listed below.

1. Ipatasertib (GDC-0068) is expected to be mild to moderate inhibitor of CYP3A *in vivo*. A clinical study in patients showed that ipatasertib (GDC-0068) at a dose of 600 mg resulted in a 2.22-fold increase in midazolam (sensitive CYP3A substrate) exposures. Ipatasertib (GDC-0068) is primarily metabolized by CYP3A, and hence, strong inhibitors and inducers of CYP3A may increase or decrease ipatasertib (GDC-0068) exposures, respectively. Therefore, the following drugs should be avoided, or used with caution, when administering ipatasertib (GDC-0068). If the use of one of these drugs is necessary, a risk/benefit assessment should be made prior to its concomitant use with ipatasertib (GDC-0068) per protocol guidelines:

- Strong CYP3A inhibitors: such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, and/or grapefruit juice or grapefruit supplements.
- Strong CYP3A inducers: such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, phenobarbital, and/or St. John's wort (hyperforin).
- CYP3A4 substrates with a narrow therapeutic index: such as, but not limited to alfentanil, astemizole, terfenadine, cisapride, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, ergot alkaloids ergotamine, and/or dihydroergotamine.

Patients should be closely monitored. Refer to the updated list of substrates, inhibitors and inducers elaborated by the U.S. Food and Drug Administration (FDA) agency for further guidance on CYP450−drug interactions, through the following link:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

2. *In vitro* studies indicated that ipatasertib (GDC-0068) was a substrate and inhibitor of P-glycoprotein (P-gp) transporter at the highest test concentration (729 µM). However, based on the parameters outlined in the U.S. FDA's Drug Interaction Studies (63) and the European Medicines Agency (EMA)'s Guideline on the Investigation of Drug Interactions (64), ipatasertib (GDC-0068) should not be a perpetrator of a P-glycoprotein mediated DDI in the intestine after a 400 mg dose.

   Additional *in vitro* transporter studies suggest that ipatasertib (GDC-0068) is a very mild inhibitor of breast cancer resistance protein, inhibitor of the organic anion transporter P1B1, OATP1B3, the multidrug and toxin extrusion protein 1 and MATE-2K. However, the clinical significance of the in vitro membrane transport interactions is currently unknown.

   An *in vitro* study showed the N-dealkylated metabolite of ipatasertib (GDC-0068) (M1) was substrate and inhibitor of organic cation transporter (OCT)1 and OCT2. However, the C_{max} of M1 following a 400 mg human dose of ipatasertib (GDC-0068) was much lower than the IC50 values reported for all transporters; thus, M1 is not expected to be a likely perpetrator of transporter-mediated DDIs.

2.8 Study Rationale

2.8.1 Global Rationale

Results from GO29227 randomized phase II trial (LOTUS) support further evaluation of first-line ipatasertib (GDC-0068) and paclitaxel for patients with metastatic TNBC in the ongoing IPATunity130 trial (NCT03337724). This study is a randomized phase III trial evaluating the

efficacy of ipatasertib (GDC-0068) and paclitaxel versus placebo and paclitaxel in patients with *PIK3CA/AKT1/PTEN*-altered TNBC or luminal metastatic breast cancer who are not suitable for endocrine therapy. However, it is also of interest to assess the potential synergy between ipatasertib (GDC-0068) and other non-taxane chemotherapy regimens in patients previously treated with a taxane-containing regimen.

These assessments are also justified by the significant synergy reported in the preclinical setting between different inhibitors of the PI3K/AKT/mTOR pathway and non-taxane chemotherapy drugs, such as eribulin, capecitabine, platinum drugs, and gemcitabine. All these chemotherapy regimens are thoroughly employed in treating patients with TNBC.

A synergy between PI3K/AKT/mTOR inhibitors and eribulin has been observed in TNBC cell lines as for the anti-proliferative, pro-apoptotic, and anti-metastatic effects (65). In these models, the combined therapy exhibited increased antitumor activity compared to single-agent treatments. Particularly, this combination is able to reduce the mammosphere formation, and markers for epithelial-mesenchymal transition (EMT) (66). It is well established that eribulin suppresses experimental metastasis of breast cancer cells, consistent with a phenotypic switch from EMT to mesenchymal-epithelial states (67).

In relation to capecitabine, 5-fluorouracil (5-FU) induced expression of the A disintegrin and metalloproteases protein 12 isoform L (ADAM12-L). The overexpression of ADAM12-L in breast cancer cells following 5-FU treatment leaded to the acquisition of resistance to 5-FU. ADAM12-L overexpression also resulted in increased levels of pAKT. Decreasing the levels of pAKT seems to restore 5-FU sensitivity in 5-FU-resistant breast cancer cells lines. On the other hand, ADAM12 knockdown reduced breast cancer cell survival and invasive abilities (68). These findings propose specific ADAM12-L inhibition could optimize 5-FU-based chemotherapy of breast cancer.

Furthermore, PI3K/AKT/mTOR inhibitors could fully restore cisplatin sensitivity in cisplatin-resistant TNBC cells lines and synergistically act with cisplatin (69). The combination significantly increased the effect on cisplatin sensitivity of each of the compounds alone. This synergistic effect has been also identified when combining PI3K/AKT/mTOR inhibitors and carboplatin (70).

Finally, preclinical data suggests that gemcitabine resistance in breast cancer cells is mainly mediated by activation of the PI3K/AKT signaling pathway, consistent with an elevated expression of pAKT gene leading to cell proliferation (71). Accordingly, targeting the PI3K/AKT/mTOR pathways may help develop effective therapies in patients with gemcitabine-resistant breast cancer.

2.8.2 Study design rationale

The open-label, non-comparative, phase IIa PATHFINDER trial aims to analyze the safety, tolerability, and preliminary efficacy of ipatasertib (GDC-0068) in combination with non-taxane

chemotherapy agents (capecitabine, eribulin, and carboplatin plus gemcitabine) in taxane-pretreated unresectable locally advanced or metastatic TNBC patients.

A run-in phase for safety and tolerability of ipatasertib (GDC-0068) in combination with standard doses of the selected non-taxane chemotherapy regimens will be conducted as an initial step of the non-comparative phase IIa in this patient population. This phase aims at evaluating and establishing the dosing schedule of ipatasertib (GDC-0068), by analyzing the toxicity profiles of each of the combined regimens.

With the Background of PAM4983g, GO29227 and IPATunity130 trial, the safe starting dose of Ipatasertib (GDC-0068) has been established as 400 mg.

2.8.3 Benefit/Risk assessment

Advanced TNBC is the subtype of breast cancer with the worst prognosis, with a median OS of only 18-21 months (1,7). Current approaches in treatment of this kind of tumors include treatment with taxenes as first-line treatment. For those tumours which present PDL1 expression, the standard treatment is nab-paclitaxel in combination with atezolizumab. Patients with *BRCA1/2* germline mutation are an exception, as olaparib has demonstrated a clear benefit in PFS for this population (34). After tumor progression at the end of the first-line treatment - and with exception to those tumours with *BRCA1/2* mutation -, besides chemotherapy, there isn't any approved targeted treatment that have shown a significant survival benefit in patients with advanced TNBC. This highlights the importance of developing new drugs and treatments for patients with a TNBC that has progressed.

With the lack of a standard therapy for patients with TNBC that has progressed after treatment with taxenes, the frequently used treatments are capecitabne, eribulin and carboplatin plus gemcitabine. These treatments have been widely tested in breast cancer and present a well-known and acceptable toxicity and safety profile.

Alterations in the PI3K signaling pathway are involved in resistance mechanisms in breast cancer, and particularly in TNBC, where 35% of TNBC patients present these alterations (45,53,54). Ipatasertib is an inhibitor of AKT, a key member of the PI3K signaling pathway, which has shown an acceptable safety profile when used as monotherapy and in combination with paclitaxel at a dose of 400 mg/day. In addition, studies with added AKT inhibitors as first-line treatment for metastatic TNBC (such as LOTUS) have shown a significant OS improvement compared to their placebo counterpart arm (described in ***Section 2.7.2.2***).

Therefore, in light of the data shown by numerous clinical trials, the benefit-risk assessment for the administration of ipatasertib in combination with capacetabine, eribulin or carboplatine plus gemcitabine, is considered positive in patients with non-resectable locally advanced or metastatic

TNBC. And given the high incidence of diarrhea observed in some studies, this study takes a preventive approach by recommending prophylactic loperamide to all patients during at least the first initial cycle of treatment (as described in ***Section 7.7.2***), as well as by reducing the dose of capecitabine taken by the patient.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

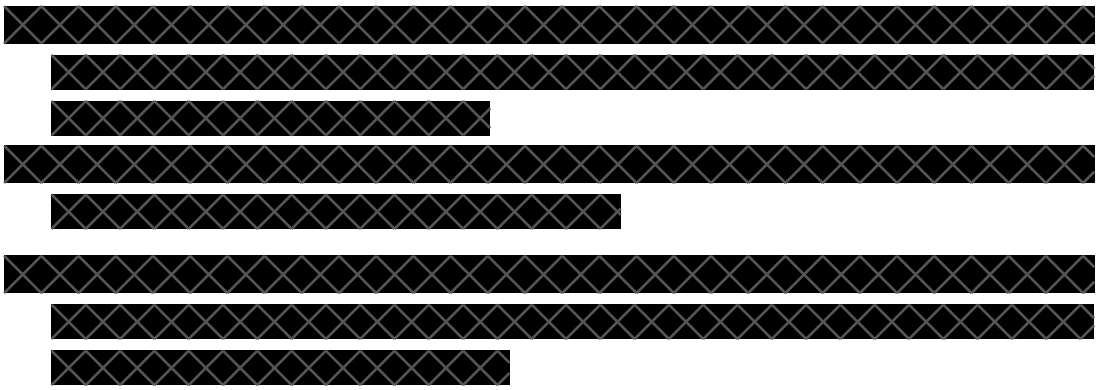
3.1.1 Primary Objective

- To evaluate the safety and tolerability of ipatasertib (GDC-0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine in the ITT population of patients with taxane-pretreated unresectable locally advanced or metastatic TNBC.

3.1.2 Secondary Objectives

- To determine the efficacy of ipatasertib (GDC-0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine in the ITT population and in each treatment arm.

3.1.3 Exploratory Objectives



3.2 Study Endpoints

3.2.1 Primary Endpoint

- Incidence of AEs as assessed by the investigator, with severity determined through the use of National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI–CTCAE) NCI-CTCAE v.5.0.

3.2.2 Secondary Endpoints

- PFS, defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined locally by the investigator through the use of Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1.
- Time to response (TTR), defined as the time from the treatment initiation to time of the first objective tumor response (tumor shrinkage of ≥ 30%) observed for patients who achieved a CR or PR, as determined locally by the investigator through the use of RECIST v.1.1.
- ORR, defined as a CR or PR, as determined locally by the investigator through the use of RECIST v.1.1.
- DoR, defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined locally by the investigator through use of RECIST v.1.1.
- CBR, defined as an objective response (CR or PR), or SD for at least 24 weeks, as determined locally by the investigator through the use of RECIST v.1.1.
- OS, defined as the time from treatment initiation to death from any cause, as determined locally by the investigator through use of RECIST v.1.1.
- Best percentage of change from baseline in the size of target tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, as determined locally by the investigator through use of RECIST v.1.1.

3.2.3 Exploratory Endpoints

- PFS, TTR, ORR, DoR, CBR, OS, and best percentage of change in target tumor lesions, as determined locally by the investigator through the use of RECIST v.1.1 in the subset of patients with [redacted] altered tumors.

- Relationship between tissue- and blood-based biomarkers and patient clinical features (e.g., baseline features) and outcome (e.g., duration of PFS).
- Changes in mutation and copy number in oncogenes, tumor suppressors, and/or other genes associated with disease progression assessed by DNA sequencing.
- Changes in levels of tumor suppressors, immune checkpoints, mitotic index, apoptotic index, and/or immune-cell infiltration assessed by IHC.
- Associations of breast cancer subtypes defined by molecular signatures with patient outcomes.

4 STUDY OVERVIEW

4.1 Study Design

This is a multicenter, open-label, non-comparative, three-arm, phase IIa clinical trial that is designed to evaluate the safety, tolerability, and efficacy of ipatasertib (GDC-0068) in combination with eribulin, capecitabine, or carboplatin plus gemcitabine for taxane-pretreated patients with unresectable locally advanced or metastatic TNBC that is not amenable to resection with curative intent.

Patients must have received at least one, but not more than two, prior chemotherapeutic regimens for treatment of unresectable locally advanced and/or metastatic disease (at least one regimen must have contained a taxane). Earlier adjuvant or neoadjuvant therapy for more limited disease will qualify as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. Therefore, exclusive prior taxane-based therapy as adjuvant or neoadjuvant treatment is also allowed if the patient had a disease-free interval of less than 12 months after completing this treatment.

Evidence of either measurable or evaluable disease as for RECIST v.1.1 is mandatory. Patients with bone-only metastases are also eligible.

After signing informed consent form (ICF) and confirmed eligibility, patients will be assigned to one of the following three treatment arms based on local investigator assessment and slots availability. We expected to recruit 18 patients in each arm. However, patients could be assigned to one of the other open treatments if one arm was stopped due to feasibility or safety reasons. At the end of the study all 54 patients will be recruited, unless all arms were discontinued.

- **Arm A**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day (noon) on Days 1-14 of each 21-day cycle plus capecitabine 1000 mg/m^2 tablets orally twice a day

(morning and evening; equivalent to 2000 mg/m^2 total daily dose), for 14 days (followed by a 7-day rest period) every 21-day cycle.

- **Arm B**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus eribulin 1.23 mg/m^2 (equivalent to eribulin mesylate at 1.4 mg/m^2) administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.
- **Arm C**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus carboplatin area under the curve (AUC)5 on Day 1 administered intravenously plus gemcitabine 1000 mg/m^2 administered intravenously over 30 minutes on Days 1 and 8, every 21-day cycle.

A run-in phase for safety and tolerability of ipatasertib (GDC-0068) in combination with standard doses of capecitabine (Arm A), eribulin (Arm B), and carboplatin plus gemcitabine (Arm C) will be conducted as an initial step of the non-comparative phase IIa in this patient population (see ***Section 6.3***).

Patients will be followed to observe if they experience any significant toxicity during the first two treatment cycles. Once the dosing schedule of ipatasertib (GDC-0068) has been established, the study enrollment will proceed including the rest of patients within each treatment arm (N = 54 patients in all arms) in order to gaining further safety and efficacy data of the combined regimens.

For estimation of PFS, TTR, ORR, DoR, CBR, OS, and best percentage of change in target tumor lesions, tumor assessment will be based on RECIST v.1.1 (See **Appendix 2**) and will be performed every six weeks (± 3 days) for the first six months and every nine weeks (± 7 days) thereafter until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. Tumor assessments will be performed on the specified schedule regardless of treatment delays. Patients who discontinue treatment without evidence of disease progression per RECIST v.1.1, in addition to post-treatment follow-up, will be followed every nine weeks (± 7 days) for tumor assessments until documented progression per RECIST v.1.1, elective withdrawal from the study, the start of new anti-cancer treatment, or study completion or termination.

Bone scans are mandatory at baseline for all patients and thereafter will be repeated every 24 weeks (± 7 days) only for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression.

Brain imaging (by magnetic resonance imaging [MRI]) during the trial should be performed in subjects with known brain metastases prior to study initiation (every six weeks [± 3 days] for first six months, then every nine weeks [± 7 days]), and those with worsening and/or new neurological symptoms.

Safety assessments will include the incidence, nature, and severity of AEs and laboratory abnormalities graded per the NCI-CTCAE v.5.0. Laboratory safety assessments will include the regular monitoring of hematology, blood chemistry, coagulation, and pregnancy test. A schedule of assessments is provided in ***Appendix 1***.

For central molecular evaluation of the [redacted]-altered status and perform exploratory studies, patients must have consented to provide sufficient newly obtained tumor biopsy tissue with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived metastatic tumor specimen only upon agreement from the Sponsor. Patients will also be given the option of providing a tissue biopsy sample obtained at disease progression for exploratory analyses; this decision will not affect overall study eligibility. Furthermore, patients have agreed to give blood samples (liquid biopsy) at the time of inclusion, after two cycles of study treatment, and upon progression or study termination. The [redacted]altered status is defined as the presence of [redacted] alterations or [redacted] as determined by any tissue- or blood-based molecular diagnostic assay (using a CLIA or equivalently accredited diagnostic laboratory). To protect the integrity of the study and minimize potential bias in evaluating clinical benefit of the patients, the results of any test about the [redacted] alteration status and any interim safety analyses will not be made known to either investigators, contract research organizations, or patients prior to RECIST progression.

4.2 Study Schedule Summary

The study will consist of a 28-days screening phase, a treatment phase, and a post-treatment follow-up phase (end of treatment [EoT] and end of study [EoS] visits) that includes safety, efficacy, and survival follow-up.

4.2.1 Screening Phase

During this phase, subject eligibility is determined, including the documentation of baseline characteristics. This phase of the study will begin once the ICF is signed by the patient and procedures to be performed are described in ***Appendix 1***. One re-screening is allowed in patients that are screening failure in this study. Patient has to reconsent ICF before any study procedure is done.

4.2.2 Treatment Phase

The study treatment period is defined as the time between the study entry and the last dose of study treatment received within the trial. A run-in phase for safety and tolerability of ipatasertib (GDC-0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine will be conducted as an initial step of the non-comparative phase IIa study that will follow scheme as outlined in ***Section 6.3.***

Patients will receive study treatment according to the protocol and will be discontinued if one of the following situations arises:

- Radiologically confirmed and documented unequivocal disease progression (with the exception of patients who develop isolated progression in the brain).
- AEs that according to the protocol or in the judgment of the investigator may cause severe or permanent harm or which rule out continuation of study drug.

  Note: See detailed criteria for study treatment discontinuation due to toxicity in ***Section 7.3.***
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Serious non-compliance with the study protocol.
- Death.
- Lost to follow-up.
- Patient withdraws consent.
- The study site or the Sponsor decides to close the study.

4.2.3 Access to Trial Intervention After End of Trial

Roche will offer continued access to IMP Ipatasertib (GDC-0068) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP Ipatasertib (GDC-0068) after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being.
- There are no appropriate alternative treatments available to the participant.

- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A participant will not be eligible to receive Roche IMP Ipatasertib (GDC-0068) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for METASTATIC TRIPLE-NEGATIVE BREAST CANCER PATIENTS .
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for METASTATIC TRIPLE-NEGATIVE BREAST CANCER PATIENTS .
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.2.4 EoT and EoS Visits

Patients discontinuing the study treatment period will enter a post-treatment follow-up period. The first safety follow-up assessment (EoT visit) will be scheduled for all patients within 30 days (± 7 days) after the last dose of study treatment. All grade ≥ 3 AEs related to IMP will be followed up by the investigator until the event or its sequelae resolve or stabilize at the level acceptable to the investigator, and the Sponsor concurs with that assessment.
Afterwards, follow-up contacts will continue every three months (± 14 days) up to the EoS and survival status and new anticancer therapy information will be collected. Telephone contact is acceptable.

The EoS is defined as the last patient last visit at the end of the follow-up period. This will be the last data collection point, which can be a clinic visit or a telephone call. EoS will occur at 12 months after the last patient included in the study, unless premature termination of the study.

5 PATIENT SELECTION

This study can fulfil its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom the protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

5.1 Target Study Population

Female patients age ≥ 18 years with taxane-pretreated unresectable locally advanced or metastatic TNBC amenable to biopsy.

Patients with either measurable or evaluable disease as per RECIST v.1.1 must have received at least one, but not more than two, prior chemotherapeutic regimens for treatment of unresectable locally advanced and/or metastatic disease (at least one regimen must have contained a taxane). Earlier adjuvant or neoadjuvant therapy for more limited disease will be considered as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy.

5.2 Inclusion Criteria

Patients must meet **ALL** of the following inclusion criteria to be eligible for enrolment into the study:

1. Signed ICF prior to participation in any study-related activities.
2. Female patients ≥ 18 years at the time of signing ICF.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
4. Life expectancy of ≥ 12 weeks.
5. Histologically confirmed TNBC per American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) criteria based on local testing on the most recent analyzed biopsy. Triple-negative is defined as <1% expression for estrogen receptor (ER) and progesterone receptor (PgR) and negative for Human Epidermal Growth Factor Receptor 2 (HER2) (0–1+ by immunohistochemistry (IHC) or 2+ and negative by *in situ* hybridization [ISH) test].
6. Unresectable locally advanced or metastatic disease documented by computerized tomography (CT) scan or magnetic resonance imaging (MRI) that is not amenable to resection with curative intent.

7. Measurable or evaluable disease as per RECIST v.1.1. Patients with only bone lesions are also eligible.

8. Refractory to or relapsed after one or two prior standard of care chemotherapy regimens for unresectable locally advanced or metastatic breast cancer (MBC). Earlier adjuvant or neoadjuvant therapy for more limited disease will be considered as one of the required prior regimens if the development of unresectable locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy.

   Note: Exclusive tumor marker elevation will not be considered sufficient for diagnosis of disease progression.

9. Prior therapy must have included a taxane in any combination or order and either in the early, locally advanced, or metastatic setting.

   Note: Exclusive prior taxane-based therapy as adjuvant or neoadjuvant treatment is also allowed if the patient had a disease-free interval of less than 12 months after completing this treatment.

10. Eligible for one of the chemotherapy options (eribulin, capecitabine, carboplatin plus gemcitabine) as per local investigator assessment and slots availability. Patients treated with (neo)adjuvant platinum salts or capecitabine and who have relapsed more than one year after the last dose of either treatment may be allowed to be included in the treatment arm based on ipatasertib (GDC-0068) in combination with carboplatin plus gemcitabine and capecitabine, respectively.

11. Previous treatment with androgen receptor antagonists, poly ADP-ribose Polymerase (PARP) inhibitors, and immunotherapy is allowed. Those patients who have previously received a PARP inhibitor will not be included in the carboplatin and gemcitabine arm unless PARP inhibitors were used in the early breast cancer setting and the period between the end of PARP inhibitor-based regimen and onset of metastatic disease is at least of 12 months.

12. Resolution of all acute toxic effects of prior anti-cancer therapy to grade ≤ 1 as determined by the NCI-CTCAE v.5.0 (except for alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).

13. Willingness and ability to provide a tumor biopsy from a metastatic site or the primary breast tumor at the time of the inclusion in order to perform exploratory studies. If not feasible, patient eligibility should be evaluated by a Sponsor’s qualified designee.

    Note: Subjects for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) may submit an archived metastatic tumor specimen only upon agreement from the Sponsor.

14. Patients agree to give blood samples (liquid biopsy) at the time of inclusion, after two cycles of study treatment, and upon progression or study termination.
15. Adequate hematologic and organ function within 14 days before the first study treatment on Day 1 of Cycle 1, defined by the following:
    a) Hematological: White blood cell (WBC) count > 3.0 x 10^9/L, absolute neutrophil count (ANC) > 1.5 x 10^9/L, platelet count > 100.0 x10^9/L, and hemoglobin > 9.0 g/dL.
    b) Hepatic: Serum albumin ≥ 3 g/dL; Bilirubin ≤ 1.5 times the upper limit of normal (× ULN) (≤ 3 x ULN in the case of Gilbert's disease); aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 2.5 × ULN (in the case of liver metastases ≤ 5 × ULN); alkaline phosphatase (ALP) ≤ 2 × ULN (≤ 5 × ULN in the case of liver and/or bone metastases ≤ 5 × ULN).
    c) Renal: Serum creatinine < 1.5 × ULN or creatinine clearance ≥ 50 mL/min based on Cockcroft−Gault glomerular filtration rate estimation.
    d) Coagulation: Partial Thromboplastin Time (PTT) (or activated Partial Thromboplastin Time [aPTT]) and International Normalized Ratio (INR) ≤ 1.5 × ULN (except for patients receiving anticoagulation therapy).

    Note: Patients receiving heparin treatment should have a PTT (or aPTT) ≤ 2.5 × 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 one to four days apart. Patients should be on a stable anticoagulant regimen.
16. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse), or to use a highly effective non-hormonal form of contraception, or two effective forms of contraception, as defined in the protocol during the treatment period and for at least 28 days after the last dose of ipatasertib (GDC-0068), three months after the last dose of eribulin, and six months after the last dose of carboplatin and gemcitabine or capecitabine, whichever occurs later, and agreement to refrain from donating eggs during this same period. Women of childbearing potential must have a negative serum pregnancy test before study treatment initiation.

5.3 Exclusion Criteria

Patients will be excluded from the study if they meet **ANY** of the following criteria:

1. Inability to comply with study and follow-up procedures.
2. Previous treatment with PI3K, mTOR, or AKT inhibitors.

3. Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (e.g., radiotherapy, stereotactic surgery), are clinically stable, and off anticonvulsants and steroids for at least two weeks before first dose of study treatment.
4. Radiotherapy or limited-field palliative radiotherapy within seven days prior to study enrolment, or patients who have not recovered from radiotherapy-related toxicities to baseline or grade ≤ 1 and/or from whom ≥ 25% of the bone marrow has been previously irradiated.
5. Major surgery (defined as requiring general anesthesia) or significant traumatic injury within 28 days of start of study drug, or patients who have not recovered from the side effects of any major surgery.
6. Grade ≥ 2 peripheral neuropathy.
7. Grade ≥ 2 uncontrolled or untreated hypercholesterolemia or hypertriglyceridemia.
8. History of type I or type II diabetes mellitus either requiring insulin or with a baseline fasting glucose > 150 mg/dL (8.3 mmol/L) or high hemoglobin A1c (HbA1c) as defined as > 7%. Patients who are on a stable dose of oral diabetes medication during at least weeks prior to initiation of study treatment are eligible for enrolment.
9. Lung disease: pneumonitis, interstitial lung disease, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia).
10. History of malabsorption syndrome or other condition that would interfere with enteral absorption or results in the inability or unwillingness to swallow pills.
11. History of or active inflammatory bowel disease (e.g., Crohn's disease and ulcerative colitis) or active bowel inflammation (e.g., diverticulitis).
12. Known hypersensitivity reaction to any investigational or therapeutic compound or their incorporated substances.
13. Patients have a concurrent malignancy or malignancy within five years of study enrollment with the exception of carcinoma in situ of the cervix, non-melanoma skin carcinoma, or stage I uterine cancer. For other cancers considered to have a low risk of recurrence, discussion with the Medical Monitor is required.
14. Current known infection with HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV). Patients with past HBV infection or resolved HBV infection (defined as having a negative hepatitis B surface antibody [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.

15. Active uncontrolled infection at the time of enrollment.
16. Congenital long QT syndrome or screening QT interval corrected using Fridericia's formula (QTcF) > 480 milliseconds.
17. Patients have an active cardiac disease or a history of cardiac dysfunction including any of the following:
    a) Unstable angina pectoris or documented myocardial infarction within six months prior to study entry.
    b) Symptomatic pericarditis.
    c) Documented congestive heart failure (New York Heart Association functional classification III- IV).
    d) Left ventricular ejection fraction (LVEF) < 50% as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO).
18. Patients have any of the following cardiac conduction abnormalities:
    a) Ventricular arrhythmias except for benign premature ventricular contractions.
    b) Supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication.
    c) Conduction abnormality requiring a pacemaker.
    d) Other cardiac arrhythmia not controlled with medication.
19. Patients have any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment contraindicate patient participation in the clinical study.
20. Treatment with strong CYP3A inhibitors or strong CYP3A inducers within 14 days or five drug-elimination half-lives, whichever is longer, prior to initiation of study treatment.
21. Pregnant, breastfeeding, or intending to become pregnant during the study or within 28 days after the last dose of ipatasertib (GDC-0068), three months after the last dose of eribulin, and six months after the last dose of carboplatin and gemcitabine or capecitabine, whichever occurs later.
22. Treatment with approved or investigational cancer therapy within 14 days prior to initiation of study drug.
23. Concurrent participation in other interventional clinical trial.

6 ASSESSMENTS AND STUDY PROCEDURES

The schedule of activities to be performed during the study is provided in the ***Appendix 1***. 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.

6.1 Patient Entry Procedures

Written ICF from the patient must be signed before performing any study procedure.

Before giving their consent, patients will be informed about the nature of the study drug and will receive pertinent information regarding study objectives, study treatment, follow-up procedures, biological samples collection and its legal implications, possible benefits, and potential risk and AEs. Patients will be also informed that they have the right to withdraw from the study at any time and for any reason, without being required to state their reasons for doing so. This decision will not affect any future medical treatment.

After receiving the document, the patient will read it (or receive information verbally in front witnesses) and will sign the approved ICF. The patient will receive a signed copy of the ICF and ICFs 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. After a failed screening attempt, one re-screening will be allowed to patient who did not meet one or more criteria required for participation in this study. A potential re-screened patient should sign a new ICF before any screening test or study related procedure is performed.

At inclusion, each patient will be given a unique patient number (UPN) for this study, provided by the Sponsor. If a patient is re-screened, her patient number will remain the same as the assigned in the initial screening. All data will be recorded in the appropriate case report form (CRF) using this identification number.

Confirmation of patient's eligibility for study participation will be recorded in the CRF. The investigator is responsible for safeguarding patient information (e.g., age, name, address, telephone number, and study identification number), ensuring access to this information by Health Authorities if necessary. These records will remain confidential for the period of time established by current legislation.

6.2 Patient Allocation

After signing ICF and confirmed eligibility patients will be assigned to one of the following three treatment arms:

- **Arm A**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day (noon) on Days 1-14 of each 21-day cycle plus capecitabine 1000 mg/m^2 tablets orally twice a day (morning and evening; equivalent to 2000 mg/m^2 total daily dose), for 14 days (followed by a 7-day rest period) every 21-day cycle.
- **Arm B**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus eribulin 1.23 mg/m^2 (equivalent to eribulin mesylate at 1.4 mg/m^2) administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.
- **Arm C**: Ipatasertib (GDC-0068) 400 mg tablets administered orally once a day on Days 1-14 of each 21-day cycle plus carboplatin AUC5 on Day 1 administered intravenously plus gemcitabine 1000 mg/m^2 administered intravenously over 30 minutes on Days 1 and 8, every 21-day cycle.

Patient allocation will be based on local investigator assessment and slots availability. We expected to recruit 18 patients in each arm. However, patients could be assigned to one of the other open treatments if one arm was stopped due to feasibility or safety reasons. At the end of the study all 54 patients will be recruited, unless all arms were discontinued.

6.3 Safety Run-In Phase

A run-in phase for safety and tolerability of ipatasertib (GDC-0068) in combination with standard doses of capecitabine (Arm A), eribulin (Arm B), and carboplatin plus gemcitabine (Arm C) will be conducted as an initial step of the non-comparative phase IIa in this patient population.

Up to three patients will be initially included in the first dosing level of 400 mg/day of ipatasertib (GDC-0068) (Dose level 1, ***Table 3***). If one significant toxicity is observed during the first 2 cycles (***Table 4***), three additional patients will be enrolled at 400 mg/day cohort to determine the number of total significant toxicities observed in six patients.

Table 3. Safety Run-In Dosing Schedule.

Continuous dosing schedule	Ipatasertib (GDC-0068)*
Dose level 1 (starting dose)	400 mg/day
Dose level 2	300 mg/day
Dose level 3	Not permitted

Continuous dosing schedule	Ipatasertib (GDC-0068)*
* In the safety run-in phase of the study, ipatasertib (GDC-0068) will be administered in combination with initial standard doses of capecitabine (Arm A), eribulin (Arm B), and carboplatin plus gemcitabine (Arm C). Dose adjustments of ipatasertib (GDC-0068) and/or chemotherapy (if toxicities are attributable to chemotherapy) will be evaluated according to the significant drug-related toxicities.	

If two or more significant toxicities (***Table 4***) are observed in three or six patients treated with 400 mg/day of ipatasertib (GDC-0068), it can be decided to evaluate 300 mg/day of ipatasertib (GDC-0068) (dose level 2) and/or to reduce the chemotherapy treatment (if toxicities are attributable to chemotherapy) according to the corresponding dose levels (***Table 7*** to ***Table 9***), following the same procedure as described for the 400 mg/day cohort (dose level 1).

If two or more significant toxicities (***Table 4***) are observed in three or six patients treated with 300 mg/day of ipatasertib (GDC-0068) and/or with chemotherapy in a lower dose level, patient enrollment will be interrupted for that treatment arm.

Table 4. Significant Toxicity Definition.

Toxicity	Any of the following criteria
Hematological	• Grade 3/4 neutropenia lasting > 7 days. • Grade ≥ 3 febrile neutropenia. • Grade ≥ 4 anemia. • Grade 4 thrombocytopenia. • Grade 3 thrombocytopenia associated with clinically significant bleeding.
Gastro-intestinal	• Grade ≥ 3 vomiting or nausea lasting ≥ 72 hours despite optimal anti-emetic therapy. • Grade ≥ 3 diarrhea lasting ≥ 72 hours despite optimal anti-diarrheal therapy.
Metabolic	• Grade 3 or asymptomatic grade 4 hyperglycemia lasting > 7 days despite optimal treatment. • Symptomatic grade 4 hyperglycemia.
Hepatic	• Grade 3 elevation of ALT or AST lasting > 7 days. • Grade 4 elevation of ALT or AST. • Grade 2 elevation of serum bilirubin lasting > 7 days. • Grade ≥ 3 elevation of serum bilirubin. • Any case of potential drug-induced liver injury that meet Hy's Law.

During the safety run-in phase of the study, patients will be evaluable if they completed at least 70% of the protocol-specified doses for each individual drug during Cycle 1. If a patient receives < 70% of the protocol-specified cumulative dose for an individual during Cycle 1 because of the study drug-related toxicity, then the toxicity will be considered a significant toxicity. If a patient receives <70% of the protocol-specified doses for an individual drug during Cycle 1 because of unrelated adverse events, non-compliance or protocol deviation, then the patient will be replaced.

The dosing schedules of ipatasertib (GDC-0068) and/or chemotherapy will be selected based on the overall evaluation of clinical data from the safety run-in phase, including toxicities, AEs/SAEs, and laboratory parameters.

Patients assigned to each cohort will remain in their study cohort during the entire study period.

Once the dosing schedules of ipatasertib (GDC-0068) and chemotherapy have been established, an early interim analysis will be performed in order to continue with the phase IIa.
The interim analysis will be performed independently in each arm after the last evaluable patient in the run-in phase has completed the two first cycles of study treatment in order to assess the toxicity profile of each regimen. This data will be shared with F. Hoffmann-La Roche Ltd.
The study enrollment will proceed finalizing the number of patients within each treatment arm in order to gaining further safety and efficacy data of the combined regimens.

6.4 Study Assessments

6.4.1 Schedule of Assessments

Study assessments are outlined in ***Appendix 1***.

6.4.2 Visit Schedule

Written patient ICF should be obtained prior to undergoing any study related procedures.

All screening tests and evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria within 28 days prior to the first administration of study medication. Tumor assessments and LVEF evaluation available and performed as part of clinical practice prior to obtain the signature of the ICF, and within 28 days prior to treatment start or within 12 weeks prior to Cycle 1 Day 1 respectively, are accepted; moreover, bone scans performed within 60 days prior to Cycle 1 Day 1 are accepted. Therefore, such evaluations are not required to be repeated during the screening period.

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.

Visits are organized in programmed cycles of 21 days (if there are no delays in treatment owing to the occurrence of an AE). All visits must occur within ± 2 working days (± 1 working day in Day 8 of each cycle) from the scheduled date, unless otherwise noted in the schedule of assessments.

Assessments scheduled for Days 1 and 8 of each cycle must be performed within 48 hours and 24 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up.

If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (e.g., within a period of ± 2 working days).

Day 8 visits can be omitted, at the Investigator's discretion, for patients enrolled in Arms B or C that permanently discontinue chemotherapy and continue with ipatasertib (GDC-0068) as single agent. However, laboratory assessments and clinical visits could be scheduled as needed for follow-up of ipatasertib (GDC-0068)-related adverse events. A telephone call may be also acceptable.

EoT visit will be performed within 30 days after last dose of study treatment. Afterwards, follow-up contacts will continue every three months (± 14 days) up to the EoS and survival status and new anticancer therapy information will be collected. Telephone contact is acceptable.

EoS will occur at 12 months after the last patient included in the study, unless premature termination of the study.

6.4.3 Medical History and Demographic Data

Demographic data, general medical history, and prior medical history of breast cancer will be collected during the screening period.

Demographic data includes age, sex, and self-reported race/ethnicity.

General medical history includes clinically significant diseases, surgical interventions, history of smoking, alcoholism, drug addiction, as well as any medications (e.g., prescribed drugs, over-the-counter drugs, medicinal plants, homeopathic remedies, or food supplements) used by the patient in the 28 days prior to screening visit.

Previous medical history of breast cancer (including prior antineoplastic treatments and procedures including radiotherapy and surgeries) will be also assessed with further detail. In particular, it will be evaluated the number of chemotherapy regimens for unresectable locally advanced or MBC, including start and stop date and best response, and the prior use of a taxane or PI3K, mTOR, or AKT inhibitors in any combination or order and either in the early, locally advanced, or metastatic setting.

Moreover, patients will complete a medication diary each day to assess the actual intake of medication taken outside of the clinic/hospital setting. Patients will receive the diary on the first day of each cycle, with site staff completing information on any prescribed medication, including the recommended dosage and route of administration. Patients should use the diary to record daily ipatasertib (GDC-0068) and capecitabine (for patients assigned to the treatment arm A) dosing, and any other medication (prescribed or over-the-counter) taken on that cycle of treatment. The intake of analgesic, anti-histamine, and loperamide medication will be reported in the relative page of the Concomitant Medications CRF.

6.4.4 Vital Signs

Vital signs will be collected during the screening period and on Days 1 and 8 of each cycle. These will include the measurement of height (only during screening), weight, respiratory rate, pulse rate, systolic and diastolic blood pressure while the patient is in a seated position after resting for at least five minutes, and oral, axillary, or tympanic temperature. Abnormal or significant changes in vital signs from baseline should be recorded as AEs, if appropriate.

6.4.5 Physical Examination

A complete physical examination will be performed during the screening period and on Day 1 of each cycle. This examination should include an evaluation of head, eyes, ears, nose, and throat as well as cardiovascular, dermatological, musculoskeletal, respiratory, digestive, genitourinary, and neurological systems. In addition, for breast cancer patients, this physical exam should also include, as part of tumor assessment, evaluation of the breast and regional lymph nodes as well as the presence and degree of increase of other lymph nodes, hepatomegaly, and splenomegaly. Limited physical exams will be performed on Day 8 of each cycle and will only focus on the following symptoms: diarrhea, nausea, vomiting, mucositis, dyspnea/cough, and skin toxicity.

Changes to abnormalities identified during the baseline period should be recorded at all subsequent physical examinations. New or worsening abnormalities should be recorded as AEs, if applicable.

6.4.6 Tumor and Response Evaluations

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation. Tumor response will be assessed for all patients, unless they withdraw from the study for any reason not attributable to disease progression confirmed radiologically or clinically as per RECIST v.1.1 criteria and who have not received an acceptable complete assessment of

the disease. The measurable and non-measurable disease must be documented at screening and be re-assessed at every tumor assessment thereafter.

Tumor assessment during the screening period should include an evaluation of all known and/or suspected lesions/sites of the disease, including color photography of skin lesions, based on the baseline assessment of target and non-target lesions according to RECIST v.1.1 criteria as the reference for comparison at each subsequent tumor assessment. The same radiographic procedure employed at screening should be used throughout the study (e.g., the use of the same contrast protocol for CT scans).

At baseline, all patients should be assessed as follows:

- **Evaluation of chest, abdomen, and pelvis:**
    - This assessment should be evaluated preferably by CT scan or MRI, since these methods are the best currently available and reproducible techniques to measure lesions selected for response assessment, within 28 days prior to the first administration of study medication.
    - In the event a positron emission tomography (PET)/CT scan is used for tumor assessments, CT portion of PET/CT is usually of lower quality, and should not be used instead of dedicated diagnostic CT. If the CT scan is of high quality, with oral and intravenous contrast, may be used with caution. Additional information from PET may bias CT assessment.
    - After baseline, this evaluation will be performed every six weeks (± 3 days) from the first dose of study treatment for the first six months and, thereafter, every nine weeks (± 7 days) until the EoS visit.

- **Brain imaging:**
    - A brain MRI will be only performed in patients with known brain metastases preceding the study inclusion within 28 days prior to the first administration of study medication.
    - After baseline, this evaluation will be performed every six weeks (± 3 days) from the first dose of study treatment for first six months, then every nine weeks (± 7 days), unless clinically suspected brain progression.

- **Bone scan:**
    - Bone scan imaging is mandatory at baseline for all patients.

- Thereafter, for patients with bone lesions identified at baseline, bone scan will be performed every 24 weeks (± 7 days), unless clinically or biochemically suspected bone progression.
- If no bone involvement is demonstrated, then it is no necessary to repeat the bone assessment unless clinically or biochemically suspected bone progression.
- If an isotope-based bone scan was performed > 28 days but ≤ 60 days prior to start of study treatment, the bone scan does not need to be repeated.

Bone scan should be used only to identify presence of bone lesions and if bone lesions are present, confirmation and accurate measurement must be done with CT scan or MRI. 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 scan or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability. Blastic bone lesions are non-measurable. If a bone scan cannot be performed during the course of the study because of the unavailability of the Tc-99m isotope, the investigator may choose an alternative imaging modality.

If clinically indicated, CT scan or MRI of other areas of disease as appropriate should be performed. Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy administration, it can be considered as a measurable lesion.

Patients who discontinue treatment without evidence of disease progression per RECIST v.1.1, in addition to post-treatment follow-up, will be followed every nine weeks (± 7 days) for tumor assessments until documented progression per RECIST v.1.1, elective withdrawal from the study, the start of new anti-cancer treatment, or study completion or termination.

Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point.

At the investigator's discretion, CT scans, MRI, and/or bone scans may be obtained at any time when clinically indicated or if progressive disease is suspected. For symptomatic deterioration attributed to disease progression, every effort should be made to document progression through the use of objective criteria per RECIST v.1.1.

6.4.7 Laboratory Assessments

Laboratory tests will be performed at the study site's local laboratory during the screening period and within 48 hours prior to Day 1 of each cycle (including Cycle 1, Day 1) following ≥ 8-hour fast. This assessment does not need to be repeated at Cycle 1, Day 1 if it was performed at screening within 48 hours prior to start of study treatment. These tests should include: hematology [hemoglobin, hematocrit, red blood cell count, platelet count, and WBC with differential count (ANC, lymphocytes, monocytes, eosinophils, and basophils)] and biochemistry with renal function analysis (serum creatinine, creatinine clearance according to the Cockcroft-Gault formula), liver function [AST, ALT, ALP, gamma-glutamyl transferase (GGT), total and direct bilirubin], amylase, lipase, glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.

In addition, the following tests are essential assessments at screening, before Cycle 1, Day 1 dosing:

- HbA1c.
- Screening viral serology: HIV, HBsAg, total HBcAb, HCV antibody; additional tests for HBV DNA or HCV RNA will be required to confirm eligibility in patients with a positive antibody result.
- Coagulation: PTT (or aPTT) and INR.

Finally, only for patients included in Arms B or C, a complete blood count [hemoglobin, hematocrit, red blood cell count, platelet count, and WBC with differential count (ANC, lymphocytes, monocytes, eosinophils, and basophils)] will be also performed within 24 hours prior to Day 8 of each cycle.

6.4.8 Home Glucose Monitoring

For any patient who initiates home glucose monitoring (see ***Section 8.4.2*** for management guidance of fasting hyperglycemia), a glucose log will be made available for capturing these results. The blood glucose log should be reviewed at each clinic visit (see ***Appendix 1***).

6.4.9 Pregnancy Tests and Assessment of Fertility

Only female patients of childbearing potential must undergo pregnancy tests done locally:

- At screening: In order to ratify eligibility, a negative serum pregnancy test must be confirmed either within 96 hours of Cycle 1, Day 1 study treatment administration, or within seven days

of Cycle 1, Day 1 (in this case, confirmed by a negative urine pregnancy test on Cycle 1, Day 1 prior to dosing).

- During study treatment: Urine/serum pregnancy tests will be performed within 48 hours of Day 1 of each following treatment cycle prior to dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. In case an additional pregnancy test is indicated during the trial, a serum test should be performed.
- At EoT visit (30 days after the last dose of study treatment).

It is not known whether ipatasertib (GDC-0068) can cross the placenta and may cause harm to the fetus when administered to pregnant women or affect reproductive capacity. Therefore, ipatasertib (GDC-0068) should not be administered to pregnant women. Women of childbearing potential should take necessary precautions to avoid pregnancy while receiving ipatasertib (GDC-0068) and for the protocol-defined period following the last dose of ipatasertib (GDC-0068). Female patients of childbearing potential must agree to use a highly effective, non-hormonal form of contraception (such as surgical sterilization), or two effective forms of contraception or true abstinence during the treatment period and within 28 days after the last dose of ipatasertib (GDC-0068), three months after the last dose of eribulin, and six months after the last dose of carboplatin and gemcitabine or capecitabine, whichever occurs later as it is described on relative Summary of Product Characteristics (SmPC).

The following highly effective methods of contraception are acceptable:

- Total abstinence: When this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment. Tubal ligation will not be considered a highly effective non-hormonal methods of contraception and will not be acceptable.

Or two of the following effective forms of contraception:

- Oral contraceptives.
- Placement of an intrauterine device or intrauterine system.
- Condom with spermicidal foam/gel/film/cream/suppository.

- Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gem/film/cream/suppository.

In case of pregnancy during treatment or within one month after the last dose of study treatment, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form as specified in ***Section 8.9***.

6.4.10 Electrocardiograms (ECGs) and Cardiac Function Assessment

All patients must have a standard 12-lead ECG and an LVEF measurement of at least 50% by ECHO (preferably) or MUGA scan at baseline.

LVEF assessment must be done within 12 weeks prior to Cycle 1, Day 1. Afterwards, cardiac function evaluation should be repeated if clinically indicated.

A 12-lead ECG should be obtained within 28 days prior to the first administration of study medication and be printed and kept with the patient's record. ECG measurements will include QT interval and QTc corrected as per QTcF. Afterwards, ECG should be repeated if clinically indicated (symptoms, use of drugs known to prolong QTc, etc.). In detail, patients using drugs known to cause QTc prolongation should be monitored closely with ECG obtained at a frequency no less than every 12 weeks.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least ten minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

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.

If at a particular post-dose timepoint the mean QTcF is > 500 ms and/or > 60 ms longer than the baseline value, another ECG must be recorded, ideally within the next five minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator.

6.4.11 ECOG performance status

Performance status will be measured using the ECOG performance status scale at screening and on Day 1 of each cycle (***Table 5***). It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

Table 5. ECOG Performance Status Scale.

Grade	Scale
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, E.G., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

(http://www.ecog.org/general/perf_stat.html)

6.4.12 Biological Samples for Exploratory Analysis

6.4.12.1 Tumor Samples

Patients must agree to provide a tumor tissue sample from a metastatic site or the primary breast tumor at the time of study entry, with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived metastatic tumor specimen only upon agreement from the Sponsor.
If feasible, patients will also be given the option of providing a tumor tissue sample from metastasis or primary breast tumor obtained at disease progression.
Exploratory studies will be performed on tumor biopsies, or formalin-fixed and paraffin-embedded (FFPE) or frozen tumor samples (blocks), or unstained glass slides.

Details on tumor tissue samples preparation, processing, storage, and shipment will be provided in a separate study manual.

6.4.12.2 Blood Samples

Blood samples are required for all patients during the screening period, after two cycles of study treatment, and upon progression or study termination.

An aliquot from any of those time-points will be preserved to collect cell-free DNA (cfDNA) analysis and compare genomic DNA data from tissue samples and cfDNA data from liquid biopsies.

Details on blood samples processing will be provided in a separate study manual.

6.4.12.3 Molecular Assessments

The multiple assays, described below, may be performed with the material derived from tumor samples and/or the blood samples collected from each patient as part of this study. We will use both a hypothesis-driven and a discovery-based approach. It is likely that not all assays described below will be performed on samples provided by each patient, possibly because of insufficient material or inadequate sample quality.

We anticipate that as molecular and genomic technologies improve, as yet unspecified technologies will be applied.

Biomarker samples (blood, plasma, and tissue) for mandatory exploratory biomarker research include, but not limited to, the following assays and assay platforms:

- Single-nucleotide polymorphisms that may impact exposure or other responses, or next-generation sequencing (NGS) results interpretation;
- Somatic mutations and copy-number variations by NGS or PCR-based methods in tumor tissue and cfDNA;
- Expression analysis of genes related to [redacted] pathway activity, immune infiltration/activation, apoptosis, and breast cancer biology (e.g., intrinsic subtypes);
- IHC-based analysis or quantitative digital IHC of tumor suppressors, such as [redacted], and markers of immune infiltration and activation, such as [redacted]

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. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Given the complexity and exploratory nature of the analyses, data derived from exploratory studies, including germline mutations, will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

7 STUDY DRUGS INFORMATION

7.1 Formulation, Packaging, and Handling

The investigational medicinal product (IMP) for this study is ipatasertib (GDC-0068). Capecitabine, eribulin, carboplatin, gemcitabine, and loperamide is a non-IMP in the study.

The IMP required for completion of this study (Ipatasertib (GDC-0068)) will be provided by F. Hoffmann-La Roche Ltd. The study site will acknowledge receipt of IMPs supplied by Roche by returning the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfill GMP (annex 13) requirements for labeling. Label text will be translated into local language.

IMPs will be disposed of at the study site according to the study site's institutional standard operating procedure with the appropriate documentation. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded throughout the course of the study.

The non-IMP used on the study such as Capecitabine, Eribulin, Carboplatin, and Gemcitabine will be provided by each investigational site if feasible.

7.1.1 Ipatasertib (GDC-0068)

Ipatasertib (GDC-0068) drug product is intended for oral administration and will be supplied as film-coated tablets 100 mg and 200 mg. The ingredients in the tablets include microcrystalline cellulose, butylated hydroxy anisole, croscarmellose sodium, colloidal silicon dioxide, povidone, stearic acid, and Opadry®II Yellow film coat.

The ipatasertib (GDC-0068) tablets are packaged in high-density polyethylene bottles with desiccant; The desiccant is part of the bottle cap. The storage condition is, "do not store above 25°C, protect from moisture". Information on the shelf life of the ipatasertib (GDC-0068) tablets is provided on the label. The IMP is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for patient use or returned to the Sponsor/Roche.

The unique patient number (UPN) should be recorded on the box label in the spaces provided at the time of assignment to patient. Ipatasertib (GDC-0068) is an agent that must be handled and administered with care. Patients should be instructed by site personnel to keep their medication in the bottles provided and not transfer it to any other container. In addition, site personnel must ensure that patients clearly understand the directions for self-medication. Patients will be instructed to bring their study drug and medication diary with them to each study visit.

Patients should be given a sufficient supply to last until their next study visit. The period between re-dispensing and last tablet consumed should not exceed one month. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned unused medication must not be re-dispensed to patient.

For additional information of the IMP, see the current ipatasertib (GDC-0068) Investigator's Brochure.

7.1.2 Chemotherapy

Chemotherapy should only be administered under the supervision of a qualified physician experienced in the appropriate use of cytotoxic medicinal products.

For information on the formulation, packaging, preparation and dispensing of each chemotherapy agent, please see the local prescribing information and relative Summary of Product Characteristics (SmPC) of capecitabine, eribulin, carboplatin, and gemcitabine.

7.2 Dosage and administration

7.2.1 Ipatasertib (GDC-0068)

Ipatasertib (GDC-0068) will be administered at the starting dose of 400 mg orally daily, beginning on Cycle 1, on Days 1−14 of each 21-day cycle until disease progression, intolerable toxicity, death, elective withdrawal from the study, or study completion or termination, whichever occurs first. Considering its co-administration with chemotherapeutic agents has not been yet investigated, ipatasertib (GDC-0068) in combination with capecitabine, eribulin, or carboplatin plus gemcitabine can be given without regard to order dosing.

For patients assigned to Arm A it is suggested to administrate ipatasertib (GDC-0068) orally daily (noon) and capecitabine orally twice daily (morning and evening).

Patients assigned to Arms B and C will receive ipatasertib (GDC-0068) prior to the intravenous infusion of eribulin and carboplatin plus gemcitabine, respectively.

Each dose of ipatasertib (GDC-0068) should be taken with a minimum of three ounces (90 mL) o [redacted] If a dose is missed (not taken within eight hours after the scheduled dosing time), the patient should resume dosing with the next scheduled dose. Missed or [redacted] doses will not be made up.

.No food or fluids [redacted] will be allowed for eight hours prior to each Day 1 study visit until after study laboratory samples for fasting glucose and fasting lipid profile, as applicable, are obtained.

7.2.2 Loperamide

Diarrhea is a common adverse event associated with ipatasertib (GDC-0068) 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 during at least the first initial cycle of treatment and may be extended to the next cycle if necessary and 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 reminder of the study using their discretion based on clinical judgments.

If diarrhea occurs despite loperamide prophylaxis, it should be managed per guidelines in ***Section 8.4.1***; upon resolution or when study treatment is restarted, loperamide prophylaxis should be considered to resume and continue based on clinical judgments (if allowed by local guidance).

7.2.3 Capecitabine

The starting dose of capecitabine is 1000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2000 mg/m^2 total daily dose), for 14 days (followed by a 7-day rest period) every 21-day cycle. Capecitabine tablets should be swallowed with water within 30 minutes after a meal.

7.2.4 Eribulin

The starting dose of eribulin as the ready to use solution is 1.23 mg/m^2 (equivalent to eribulin mesylate at 1.4 mg/m^2) which should be administered intravenously over 2 to 5 minutes on Days 1 and 8 of every 21-day cycle.

7.2.5 Carboplatin plus Gemcitabine

Carboplatin AUC5 will be administered intravenously on Day 1 plus gemcitabine 1000 mg/m^2 administered intravenously over 30 minutes on Days 1 and 8, every 21-day cycle.

7.3 Treatment Modification

Safety and tolerability of all patients will be closely monitored throughout study treatment and the follow-up period using the NCI-CTCAE v.5.0. Patients will be assessed in order to detect any AEs before administering new study treatment during each treatment visit. Treatment will only be administered if clinical evaluation and local laboratory test results are acceptable.

7.3.1 General Guidelines

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study treatment may need to be adjusted as described in the following Sections.

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 CRF. Reasons for not adhering to the following guidance should also be documented in the patient's chart. Sites are strongly encouraged to reach out to the Medical Monitor for any guidance on this matter.

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

- Study treatment (ipatasertib [GDC-0068], chemotherapy, or both) may be interrupted to manage toxicity. A dosing gap of up to three consecutive weeks is permitted. Dose hold for longer than three weeks for a treatment-related AE will require permanent discontinuation of the attributable treatment component (ipatasertib [GDC-0068], chemotherapy, or both).
- Patients who have both ipatasertib (GDC-0068) and chemotherapy treatments interrupted for more than consecutive 21 days for a treatment-related AE will require permanent discontinuation and will be considered off study. Treatment resumption for patients recovering from treatment-related toxicity after consecutive 21 days of treatment interruption but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion after Sponsor consultation.
- Treatment with chemotherapy always guides the first day of each cycle.
- If the treatment with chemotherapy is temporarily interrupted due to toxicity and the initiation of the new cycle is delayed, new cycle Day 1 clinical visits and study procedures (e.g., physical examination, ECOG performance status, ECG, blood chemistry, and hematology)

may also be omitted if performed within seven days prior to study drug resumption. However, laboratory assessments and clinical visits should be scheduled as needed for follow-up of AEs. If treatment delay is required due to hematologic toxicities, the frequency of blood count assessments should be increased as clinically indicated. In addition, tumor assessment according to ***Appendix 1*** should not be delayed. Once the toxicity has resolved to the required level, study treatment and study procedures will be resumed, according to the original study cycle day count.

- If the treatment with ipatasertib (GDC-0068) cannot be resumed on the first day of the cycle, the patient may continue with chemotherapy if medically appropriate (per investigator discretion). Ipatasertib (GDC-0068) omitted doses will not be replaced within the same cycle.
- Arm A, B, and C: If any of chemotherapy treatments cannot be administered on the first day of the cycle, delay treatment with ipatasertib (GDC-0068) and chemotherapy concurrently for up to seven days shifting the Day 1 within the same cycle. In this way, the study cycle will be restarted such that administration of ipatasertib (GDC-0068) in combination with chemotherapy agents remain synchronized.
- Arm B: If eribulin cannot be administered on Day 8 of the cycle, the interrupted dose of eribulin may be administered later in the same cycle and may be delayed for a maximum of one week. If this eribulin dose is finally administered, treatment with ipatasertib (GDC-0068) will be continued until Day 21 of this cycle and Day 1 of subsequent cycle will be delayed one week. If during two consecutive cycles, eribulin Day 8 dose is delayed, eribulin dose should be resumed at one dose level below the previous dose according to ***Table 8*** in the subsequent cycle.
- Arm C: If gemcitabine cannot be administered on Day 8 of the cycle, this omitted dose will not be replaced within the same cycle.
- Patients whose treatment is interrupted or permanently discontinued due to an AE, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first, which includes all study assessments appropriate to monitor the event.
- 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.

7.3.2 Ipatasertib (GDC-0068): Dose Interruptions

Ipatasertib (GDC-0068) treatment may be temporarily interrupted in patients who experience toxicity considered to be related to study drug. In the event of multiple toxicities, dose interruption should be based on the worst toxicity observed. Patients are to be instructed to contact investigator as soon as any adverse sign or symptom occurs.

During ipatasertib (GDC-0068) treatment interruption due to drug-related toxicity, a patient will miss all subsequent ipatasertib (GDC-0068) planned doses within that same cycle or even delay the initiation of the subsequent cycle. However, if the ipatasertib (GDC-0068)-related AE recovers before Day 14 of the same cycle, re-dosing is allowed in that cycle. Ipatasertib (GDC-0068) omitted doses will not be replaced within the same cycle.

If a toxicity is considered to be due solely to ipatasertib (GDC-0068), chemotherapy may be administered if there is no contraindication.

If ipatasertib (GDC-0068) has been withheld for more than 21 consecutive days (as measured from the first day of interruption of scheduled ipatasertib [GDC-0068] dosing) because of treatment-related toxicity, the patient should be discontinued from ipatasertib (GDC-0068) but may continue on study with chemotherapy alone. However, if, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming ipatasertib (GDC-0068) after a hold of

more than 21 consecutive days, study drug may be restarted with the approval of the Medical Monitor.

7.3.3 Ipatasertib (GDC-0068): Dose Modifications

If the patient does not tolerate the daily dosing of ipatasertib (GDC-0068), dosing with food may be used to alleviate gastrointestinal symptoms, including nausea, vomiting, and/or diarrhea.

No more than two dose reductions of ipatasertib (GDC-0068) per patient will be allowed (See ***Table 6)***. Any patient requiring an ipatasertib (GDC-0068) dose reduction below 200 mg/day should discontinue the ipatasertib (GDC-0068) treatment permanently but may continue on the active treatment phase of the study receiving chemotherapy as per the investigator's discretion.

Once ipatasertib (GDC-0068) dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not permitted for ipatasertib (GDC-0068).

Table 6. Dose Reductions for Ipatasertib (GDC-0068).

Dose Level [1]	Ipatasertib (GDC-0068)

Starting dose	400 mg/day
First dose reduction	300 mg/day
Second dose reduction	200 mg/day
Third dose reduction	Not permitted
[1] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.	

7.3.4 Chemotherapy: Dose Interruptions and Modifications

The amount of capecitabine, eribulin, and gemcitabine is calculated according to the patient's body surface area (BSA). Weight and height should be recorded at baseline and the BSA calculated, thereafter at every scheduled visit for all patients should be re-weighed. The amount to be administered must be recalculated if the patient's body weight has changed by > 10% (increased or decreased) from baseline. Re-calculation based upon smaller changes in body weight or BSA are at investigators' discretion. The carboplatin dose is calculated using the Calvert formula.

Dose modifications for chemotherapy agents will be performed as clinically appropriate, based on the investigator's medical judgment. Details in this section can be used as guidance; however, only the specific dose levels shown should be mandatory used (***Table 7*** to ***Table 10***).

Once chemotherapy dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not permitted for chemotherapy.

If the treatment with chemotherapy has been withheld for more than 21 consecutive days (as measured from the first day of interruption of scheduled chemotherapy dosing) because of treatment-related toxicity, the patient should be discontinued from chemotherapy, but may continue on study with ipatasertib (GDC-0068) alone. However, if, in the judgment of the investigator, the patient is likely to derive clinical benefit from resuming chemotherapy after a hold of more than 21 consecutive days, study drug may be restarted with the approval of the Medical Monitor.

Table 7. Dose Reductions for Capecitabine.

Dose Level [1]	Capecitabine
Starting dose	2000 mg/m^2
First dose reduction	75%
Second dose reduction	50%

Dose Level [1]	Capecitabine
Third dose reduction	Not permitted
[1] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.	

The administration of capecitabine should be delayed on Day 1 of each cycle for any of the following:

- ANC < 1.5 x 10^9/L complicated or not by fever or infection.
- Platelets < 100.0 x 10^9/L.
- Grade 3 or 4 non-hematologic toxicities.

No adjustment to the starting dose of capecitabine is recommended in patients with mild renal impairment (creatinine clearance = 51 to 80 mL/min [Cockcroft and Gault]). In patients with moderate renal impairment (baseline creatinine clearance = 30 to 50 mL/min), a dose reduction to 75% of the capecitabine starting dose is recommended.

Table 8. Dose Reductions for Eribulin.

Dose Level [1]	Eribulin
Starting dose	1.23 mg/m^2 (1.4 mg/m^2 eribulin mesylate)
First dose reduction	0.97 mg/m^2 (1.1 mg/m^2 eribulin mesylate)
Second dose reduction	0.62 mg/m^2 (0.7 mg/m^2 eribulin mesylate)
Third dose reduction	Not permitted
[1] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.	

The administration of eribulin should be delayed on Day 1 or Day 8 of each cycle for any of the following:

- ANC < 1.0 x 10^9/L complicated or not by fever or infection.
- Platelets < 75.0 x 10^9/L.
- Grade 3 or 4 non-hematologic toxicities.

Table 9. Dose Reductions for Carboplatin plus Gemcitabine.

Dose Level [1]	Carboplatin	Gemcitabine
Starting dose	AUC5	1000 mg/m^2
First dose reduction	AUC4	750 mg/m^2
Second dose reduction	Not permitted	500 mg/m^2
Third dose reduction	Not permitted	Not permitted
[1] If the patient continues to experience specified drug-related adverse events after the second reduction, the treatment should be discontinued.		

The administration of carboplatin or gemcitabine should be delayed on Day 1 of each cycle for any of the following:

- ANC < 1.5 x 10^9/L complicated or not by fever or infection.
- Platelets < 100.0 x 10^9/L.
- Grade 3 or 4 non-hematologic toxicities.

Day 8 of gemcitabine treatment may be given according to the ***Table 10***

Table 10. Gemcitabine Dose on Day 8.

ANC		Platelets	Gemcitabine
≥ 1.0 x 10^9/L	And	> 100.0 x 10^9/L	1000 mg/m^2
0.5-0.9 x 10^9/L	Or	75.0-100.0 x 10^9/L	750 mg/m^2
< 0.5 x 10^9/L	Or	< 75.0 x 10^9/L	Not permitted
ANC = absolute neutrophil count.			

7.4 General concomitant medication and additional assistance guidelines

Concomitant treatment and prior medication are defined as non-IMP. Concomitant treatment includes any prescribed medication or phytotherapy between the 28 days prior to the administration of the first treatment dose and the last safety visit during treatment period. All concomitant treatments will be recorded. After this time, information will only be collected on any anti-cancer drugs taken by the patient until end of study.

Information on concomitant medication will include start date, end date, brand or generic name, route of administration, dose, and treatment indication.

The following concomitant treatments are permitted during the study:

1. Oral contraceptives, as allowed per local guidelines.
2. Pre-medication with steroids, antihistamines, antipyretics, and/or analgesics (e.g., prior to scans or chemotherapy administration), and steroids used on a single day to manage infusion-related reactions or allergic reactions.
3. Prophylactic loperamide is recommended for all patients during at least the first initial cycle of treatment and may be extended to the next cycle (if necessary and if allowed by local guidance, except when the Medical Monitor approves omission). Patients who experience diarrhea should be on treatment doses of loperamide per the management guidelines provided in ***Section 8.4.1***; 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.
4. Erythropoiesis-stimulating agents (ESA) are allowed (such as Procrit®, Aranesp®, Epogen®) for the supportive treatment of anemia. Blood transfusions are permitted during the study.
5. The prophylactic use of granulocyte-colony stimulating factors (G-CSF; GM-CSF) is not allowed during the first treatment cycle but can be used for cases of neutropenia arising during treatment, in accordance with the National Comprehensive Cancer Network (NCCN) guidelines.
6. Bisphosphonate therapy or RANKL inhibitor therapy (e.g., zoledronic acid and denosumab) used specifically to prevent skeletal events.
7. Luteinizing hormone-releasing hormone or gonadotropin-releasing hormone agonists for ovarian function preservation are allowed.
8. Prophylactic or therapeutic anticoagulation therapy according to Inclusion Criteria #14.d) (please refer to ***Section 5.2***).
9. Any medications deemed necessary to ensure patient safety and well-being may be administered at the discretion of the investigator with the exception of prohibited therapies described below.

7.5 Prohibited Concomitant Medication

Use of the therapies described below is prohibited during the study treatment period:

1. Investigational therapy (other than protocol-mandated study treatment) is prohibited within 14 days prior to initiation of study treatment and during study treatment. Patients are not allowed to participate in other clinical trials while they are participating in the PATHFINDER trial.
2. Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, and radiotherapy) is prohibited for various time periods prior to starting study treatment, depending on the agent (See ***Section 7.4***), and during study treatment, until disease progression is documented and the patient has discontinued study treatment, with the exception of palliative radiotherapy under certain circumstances (See ***Section 7.8*** for details).
3. Any cancer related surgery is prohibited throughout the duration of the active treatment phase of the study.
4. Chronic use of a strong CYP3A inhibitor or inducer, or sensitive CYP3A substrates with a narrow therapeutic window that are deemed not permissible by the Medical Monitor after enrollment (refer to the guidance in ***Section 7.6***).
5. Vaccination with a live vaccine.

7.6 Medications Given with Precaution

Although not prohibited, the following drugs should be avoided or temporarily used with precaution. Please, refer to the following webpage (https://drug-interactions.medicine.iu.edu/Main-Table.aspx) for a more exhaustive list.

1. Strong CYP3A inhibitors, such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, and/or voriconazole.
2. Strong CYP3A inducers, such as, but not limited to, rifampin, carbamazepine, rifapentine, phenytoin, and/or phenobarbital.
3. CYP3A 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.
4. Patients who require short-term use of a strong CYP3A inhibitor or inducer or use of sensitive CYP3A substrates with a narrow therapeutic window for medical treatment (e.g., an alternative treatment cannot be used) must exercise caution and all study treatment should be temporarily held until at least seven days after the last dose of these drugs.
5. If daily systemic steroids are initiated for treatment of any toxicity or other condition, they must be tapered to ≤ 10 mg/day oral prednisone or equivalent before ipatasertib (GDC-0068) can be resumed.

6. Patients using drugs known to cause QTc prolongation should be monitored closely with ECGs performed at a frequency no less than every 12 weeks.

7.7 Herbal Therapies and Prohibited Food

1. Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug−drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.
2. 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.
3. Consumption of St. John's wort (hyperforin), 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.

7.8 Cautionary Therapy

1. Palliative radiotherapy (e.g., treatment of known bone 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).
    - All study treatment during palliative radiotherapy should be temporarily held for at least seven days before and after the procedure. For single-day radiotherapy, this hold may be shorter, if discussed by the investigator with, and approved in advance by, the Medical Monitor.
2. Surgery as part of medical treatment in the absence of radiographic disease progression must exercise with caution. All study treatment should be temporarily held for at least seven days before and after the procedure. For minor surgeries, this hold may be shorter, if discussed by the investigator with, and approved in advance by, the Medical Monitor.

7.9 Medication Errors and Overdose

Medication errors may result in this study from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength, drug misuse or drug abuse. Patient medication errors should be recorded in the relevant section in the CRF. In

the event of an error in the administration of the medication, the Sponsor should be informed immediately.

Medication errors must be reported irrespective of the presence of an associated AE, including:

- Medication errors involving patient exposure to the IMP.
- Drug misuse or drug abuse
- Any possible medication errors or use of the medication not defined in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the AE page and should be reported immediately to the Sponsor as a SAE.

Regarding ipatasertib (GDC-0068), in Study PAM4743g (single-agent, dose-escalation study in patients with advanced solid tumors), MTD was exceeded at 800 mg with two DLTs of grade 3 asthenia and grade 3 nausea. Cases of overdosing should be managed in accordance with best medical practice.

7.10 Compliance

At the beginning of each cycle patients will be required to return the used package of ipatasertib (GDC-0068) and capecitabine.

Investigator should check compliance for chemotherapy as well as the completed patient diary for ipatasertib (GDC-0068) and capecitabine accountability.

Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.

To be considered compliant, each study patient must have received at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration. Dose adjustments must follow instructions provided in the ***Section 7.3.***

7.11 Drug Storage and Drug Accountability

Storage conditions stated in the Study Reference Safety Document (e.g., SmPC, or Local Product Document) may be superseded by the label storage information.

Investigators and site staff are reminded to continuously monitor room storage temperatures and ensure that thermometers are working correctly as required for proper storage of IMP. These

include thermometers for both the room storage and refrigerator storage. Any temperature excursions must be reported immediately to the Sponsor and documented. Once a deviation is identified, the IMP must be quarantined and not used until the Sponsor provides documentation of permission to use the IMP.

At the end of the trial, the Sponsor will provide instructions as to disposition of any unused IMP. If the Sponsor authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the Sponsor. Destruction must be adequately documented.

Ipatasertib (GDC-0068) tablets must be stored in their original container according to labelled storage conditions.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

Accurate records of all study drugs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Accountability Log. In particular, to ensure adequate records, ipatasertib (GDC-0068) tablets will be accounted for as instructed by the Sponsor/Roche. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

8 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

Safety assessments will consist of monitoring and recording protocol-defined AEs, adverse events of special interest (AESIs), and SAEs; measurement of protocol-specified hematology, clinical chemistry, measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

The Sponsor or its designee is responsible for reporting relevant SAEs to competent authorities, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonization (ICH) guidelines, European Clinical Trials Regulation (Regulation (EU) No 536/2014), and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities within seven calendar days after being notified of the event. The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central

Institutional Review Boards (IRBs)/ECs by a written safety report within 15 calendar days of notification.

8.1 AEs Definitions

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an IMP, regardless of whether it is considered related to the IMP or not.

An abnormal test finding should only be reported as an AE if meets any of the following criteria:

- Is associated with accompanying symptoms and a general diagnostic term, including the symptoms and the abnormal test finding, cannot be defined.
- Requires additional diagnostic testing or medical/surgical intervention, leads to a change in study drug(s) dosing or discontinuation from the study.
- Needs additional concomitant drug treatment.
- Is considered to be an AE by the investigator or by the Sponsor.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

The causal relationship between an AE and the IMP will be defined as follows:

- Unrelated: The temporal association between the AE and the administration of the IMP makes a causal relationship unlikely, or the patient's clinical state or the study procedure/conditions provide a sufficient explanation for the AE.
- Related: The temporal association between the AE and the administration of the IMP makes a causal relationship possible, and the patient's clinical state or the study procedure/conditions do not provide a sufficient explanation for the AE.

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the IMP. If the investigator does not know whether or not the IMP caused the event, then the event will be handled as "related to IMP" for reporting purposes.

The descriptions and grading scales found in the revised NCI-CTCAE v.5.0 will be utilized for all toxicity reporting. A copy of the NCI-CTCAE v.5.0 can be downloaded from the CTEP website: (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it meets one of the criteria for SAEs, listed below. Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

8.2 SAEs

Per definition, a SAE is defined as any AE that either:

- Results in death (e.g., the AE actually causes or leads to death).
- Is life-threatening (e.g., the AE, in the view of the investigator, places the patient at immediate risk of death when it occurs).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person ability to conduct normal life functions).
- Constitutes a congenital anomaly/birth defect (in a neonate/infant born to a mother exposed to the IMP.

Definition of life-threatening: An AE is life-threatening if the patient was at immediate risk of death from the event as it occurred, e.g., does not include an event that might have caused death if it had occurred in a more serious form. For instance, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

Definition of hospitalization: AEs requiring hospitalization should be considered serious. In general, hospitalization means that the patient has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment which would not have been appropriate at the study site. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered as serious.

Hospitalization for elective surgery or routine clinical procedures, which are not the result of an AE, need not to be notified according to immediate reporting criteria. If anything untoward is reported during any procedure, this must be reported as an AE and either 'serious' or 'non-serious' attributed according to the usual criteria.

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE not to be notified according to immediate reporting criteria. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality).
- Social admission (e.g., patient has no place to sleep).
- Administrative admission (e.g., for yearly physical examination).
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol).
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Definition of clinically/medically significant event: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or

the development of drug dependency or drug abuse. Clinically/medically significant events MUST be reported as SAEs.

In this clinical trial and as defined in this protocol, SAEs and hospitalizations unequivocally and solely related to established tumor disease progression will NOT be treated as SAEs for reporting obligations.

8.3 AESIs to Report Immediately

AESIs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). Please, refer to ***Section 8.6***, for reporting instructions.

AESIs for this study include:

- Suspected transmission of an infectious agent by the study drug, as defined below
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Cases of potential drug-induced liver injury (DILI) as follows:
    - AST and/or ALT elevations >3 times the ULN with concurrent elevation of total bilirubin (TBL) > 2 times the ULN as defined by Hy's Law (see ***Appendix 3***) (or clinical jaundice if TBL measures are not available), except in patients with documented Gilbert's syndrome. For patients with Gilbert's syndrome, elevation of direct bilirubin >2 times the ULN should be used instead.
- Grade ≥ 3 Hyperglycemia.
- Grade ≥ 3 ALT/AST elevations.
- Grade ≥ 2 colitis/enterocolitis.
- Grade ≥ 3 diarrhea.
- Grade ≥ 3 rash.
- Grade ≥ 2 pneumonitis.

All SAEs/AESIs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the patient's participation in the study, must be followed until any of the following occurs:

- The event resolves.
- The event stabilizes.
- The event returns to baseline, if a baseline value/status is available.
- The event can be attributed to agents other than the IMP or to factors unrelated to study conduct.

It becomes unlikely that any additional information can be obtained (patient or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

8.4 AEs Management Guidelines

8.4.1 Diarrhea Management Guidelines

Treatment modifications for diarrhea (any grade), when it occurs, should be instituted as early as possible. As shown in ***Table 11***, 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 (GDC-0068) with food, avoiding lactose-containing foods, and hydrating with 8−10 glasses per day (~355 mL/glass) of electrolyte-containing clear liquid, such as broth or low-calorie drinks.

For diarrhea grade ≥ 2 that persists for more than five days, despite treatment with anti-diarrheal agent(s) and/or withholding dosing of ipatasertib (GDC-0068), 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, etc.]). 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 chemotherapy agents should be maintained as tolerated. Dose reductions of ipatasertib (GDC-0068) will be by one level at a time (e.g., 400 mg to 300 mg; 300 mg to 200 mg) as outlined in ***Section 7.3.3.*** If grade ≥ 2 diarrhea persists following dose reductions of ipatasertib (GDC-0068) to 200 mg daily and with maximum treatment for diarrhea, ipatasertib (GDC-0068) should be discontinued. Chemotherapy dose reduction or discontinuation should be considered for diarrhea grade ≥ 3 and when diarrhea persists even after ipatasertib (GDC-0068) discontinuation.

Table 11. Diarrhea Management Guidelines.

Severity of Diarrhea [1]	Management Guideline
Prevention	• All patients are mandated to receive loperamide (2 mg twice a day or 4 mg once a day) as prophylaxis for diarrhea during at least the first initial cycle of treatment and may be extended to the next cycle if necessary (if necessary and if allowed by local guidance). If there are clinical concerns that preclude the use of loperamide prophylaxis in Cycle 1, discussion with the Medical Monitor is required. Loperamide dose adjustment may be made per investigator discretion after discussion with the Medical Monitor. • After the first cycle, investigators are encouraged to continue this dosing for the remainder of the study using their discretion as clinically indicated.
Grade 1 Increase of < 4 stools per day over baseline; mild increase in ostomy output compared with baseline	• Continue study drugs at the current dose level. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every four 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 (~355 mL/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	• Interrupt ipatasertib (GDC-0068) until diarrhea improves to grade 1 or better. Ipatasertib (GDC-0068) can be resumed at the same dose or one dose lower per investigator's evaluation upon improvement to grade 1 or better. • For recurrent grade 2 diarrhea, reduce ipatasertib (GDC-0068) by one (or one additional) dose level. • Rule out infectious etiology. • Manage with loperamide as early as possible 4 mg initially and then 2 mg every four 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 (~355 mL/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

Severity of Diarrhea [1]	Management Guideline
	limited to Lomotil®, codeine, or octreotide, or as per institutional guidelines. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.
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	• Interrupt ipatasertib (GDC-0068) and chemotherapy until diarrhea improves to grade 1 or better. Ipatasertib (GDC-0068) can be resumed at one dose lower. • For recurrent grade 3 diarrhea, reduce ipatasertib (GDC-0068) by one (or one additional) dose level. Consider reducing chemotherapy by one dose level when treatment is restarted. • Rule out infectious etiology. • Treat per grade 2 management guidelines and supportive care. • Upon resolution, loperamide prophylaxis can be considered and continues as clinically indicated, if allowed by local guidance.
Grade 4 Life-threatening consequences; urgent intervention indicated	• Permanently discontinue ipatasertib (GDC-0068). • Interrupt chemotherapy until diarrhea improves to grade 1 or better. Consider resuming chemotherapy regimen by one dose level lower or discontinuing chemotherapy per investigator's discretion. • Rule out infectious etiology. • Treat per grade 2 management guidelines and supportive care.
ADL = activities of daily living; BID= twice a day; NCI-CTCAE v.5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; QD = once a day. [1] Diarrhea, as defined by NCI-CTCAE v.5.0, a disorder characterized by frequent and watery bowel movements.	

8.4.2 Fasting Hyperglycemia

Because the PI3K-AKT-mTOR pathway is involved in glucose metabolism, inhibition of this signaling network and its target mTOR can cause hyperglycemia, which is a toxicity common to the class of PI3K-AKT-mTOR inhibitors. Ipatasertib (GDC-0068)-induced hyperglycemia is associated with transient insulin concentration changes and is generally asymptomatic.

Hyperglycemia, including cases of grade 3, grade 4, and a single case of grade 5 hyperglycemia, has been reported in patients receiving ipatasertib (GDC-0068) treatment. Isolated cases of hyperglycemia associated with ketoacidosis or hyperosmolar conditions resulting in dehydration and renal insufficiency have also been observed, particularly in diabetic patients.

Fasting is defined as abstaining from food and drink (with the exception of water) for at least eight hours. In general, patients with diabetes either requiring insulin therapy or with a baseline fasting glucose > 150 mg/dL (8.3 mmol/L) or high hemoglobin A1c as defined as > 7%, suggesting poorly controlled diabetes, should be excluded from studies with ipatasertib (GDC-0068). Fasting glucose levels should be carefully monitored per protocol guidelines. Patients should be instructed to report symptoms associated with hyperglycemia such as thirst, frequent urination, and blurred vision. Hyperglycemia should be managed per institutional standards of care, and per protocol guidelines. Use of oral anti-hyperglycemic agents (e.g., metformin) for patients experiencing grade ≥ 2 hyperglycemia should be considered. For grade ≥ 2 hyperglycemia, ipatasertib (GDC-0068) dosing may be interrupted or reduced per protocol guidelines.

To diminish the risk of hypoglycemia, insulin should not be administered for asymptomatic hyperglycemia of any grade. Moreover, in the event of ipatasertib (GDC-0068) 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.

Dose modification guidelines for fasting hyperglycemia attributable to study treatment are outlined below (See ***Table12***) 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 CRF will be limited to values which result in intervention.

Table12. Fasting Hyperglycemia Management Guidelines.

Fasting Glucose Values	Management Guideline
Fasting glucose value > ULN to 160 mg/dL (8.9 mmol/L) [1]	• Continue ipatasertib. • Provide patient with education on a diabetic diet and consider home glucose monitoring. • Consider oral anti-diabetic medications (e.g., metformin).

Fasting Glucose Values	Management Guideline
Fasting glucose value >160 to 250 mg/dL (> 8.9−13.9 mmol/L) [1]	• Interruption of ipatasertib until fasting glucose values return to ≤ 160mg/dL (8.9 mmol/L). • Encourage a diabetic diet and 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 (see ***Section 7.3.3*** for further details). • If the patient previously has not been receiving any oral antidiabetic medication, ipatasertib may be resumed at the previous dose level with initiation of oral anti-diabetic medication.
Fasting glucose value 250 to 500 mg/dL (> 13.9−27.8 mmol/L) [1]	• Interrupt ipatasertib until fasting glucose values return to ≤ 160 mg/dL (8.9 mmol/L). • Encourage a diabetic diet and initiate home glucose monitoring. • Treat hyperglycemia as per standard of care, noting risk of hypoglycemia if insulin is used. • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • 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 fasting glucose value exceeds 250 mg/dL (13.9 mmol/L) again, the dose of ipatasertib should be reduced by one dose level when treatment is restarted (see ***Section 7.3.3*** for further details).
Fasting glucose value > 500 mg/dL (> 27.8 mmol/L) [1]	• Interrupt ipatasertib until fasting glucose values return to ≤ 160 mg/dL (8.9 mmol/L). • Encourage a diabetic diet and initiate home glucose monitoring. • Treat hyperglycemia per standard of care, noting risk of hypoglycemia if insulin is used. • Start (or increase dose of) oral anti-diabetic medications (e.g., metformin). • Assess for volume depletion and appropriate intravenous or oral hydration. • Reduce ipatasertib by one dose level when treatment is restarted (see ***Section 7.3.3*** for further details). • If fasting glucose value exceeds 500 mg/dL (27.8 mmol/L) again, permanently discontinue ipatasertib.
ULN = upper limit of normal. [1] Note: For all grades, the patient should receive education on a diabetic diet.	

8.4.3 Nausea and/or Vomiting

Dose reductions for nausea and/or vomiting should occur only if the symptoms persist despite a minimum of two treatments with adequate (combination) anti-emetic treatment(s), including ondansetron and other anti-emetics (e.g., prochlorperazine or metoclopramide per institutional guidelines). Dose modification and symptom management guidelines for persistent nausea and/or vomiting attributable to ipatasertib (GDC-0068) are outlined in ***Table 13***.

Table 13. Nausea and vomiting management guidelines.

Severity of Nausea and/or Vomiting	Management Guideline
Grade 1	• Continue study drugs. • Provide supportive care as needed.
Grade 2	• Continue study drugs. • Provide maximum supportive care as needed per local guidelines, with a minimum of two anti-emetics, including ondansetron.
Grade ≥ 3	• Interrupt ipatasertib (GDC-0068) and chemotherapy 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 (GDC-0068) should be reduced by one dose level when treatment is restarted. Chemotherapy dose may also be reduced by one level if recurrent grade 3 nausea or vomiting occurs after dose reduction of ipatasertib (GDC-0068) has occurred.

8.4.4 Rash

Ipatasertib (GDC-0068) should be permanently discontinued for rash associated with Stevens-Johnson syndrome, toxic epidermal necrolysis, or other suspected severe hypersensitivity or allergic reaction. Dose modification and symptom management guidelines for skin toxicity attributable to study treatment are shown in ***Table 14***.

Table 14. Rash Management Guidelines.

Severity of Rash	Management Guideline
Grade 1	• Continue study drugs.

	• Consider topical steroids.
Grade 2	• Interrupt ipatasertib (GDC-0068) treatment until resolution to grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical steroids. • Consider treatment of rash with oral steroids.
Grade 3	• Interrupt ipatasertib (GDC-0068) treatment until resolution to grade 1 or better or the toxicity is no longer clinically significant. • Treat rash with topical and systemic steroids. • Consider dermatological consultation and skin biopsy. • If the skin toxicity resolves to grade 1 or better or is no longer clinically significant within 21 days, following completion of the steroid taper, ipatasertib (GDC-0068) 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 three weeks, or grade 3 rash recurs, permanently discontinue ipatasertib (GDC-0068).
Grade 4	• Ipatasertib (GDC-0068) should be permanently discontinued. • Administration of systemic steroids (oral or intravenous) is recommended. • Consider dermatological consultation and skin biopsy.

8.4.5 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 (GDC-0068). Every effort should be made to determine the etiology of dyspnea and changes in pulmonary function (See ***Table 15***).

Table 15. Pneumonitis Management Guidelines.

Severity of Pneumonitis	Management Guideline
Grade 1	• Continue study drugs. • Perform CT scan and PFTs. Repeat CT scan every eight weeks until a return to baseline.

Severity of Pneumonitis	Management Guideline
Grade 2	• Interrupt ipatasertib (GDC-0068) and chemotherapy treatments until improvement to grade 1 or better. Consider resuming ipatasertib (GDC-0068) and chemotherapy at same dose level or one dose level below the previous dose per investigator's assessment. • If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe systemic steroids as clinically indicated. • Perform CT scan and PFTs. Repeat CT scan every four weeks until a return to baseline. • For recurrent non-infectious grade 2 pneumonitis, ipatasertib (GDC-0068) must be resumed at one dose level below the previous dose. Consider resuming chemotherapy at same dose or one dose below the previous per investigator's assessment. • Discontinue ipatasertib (GDC-0068) if recovery to grade 1 or better is not evident within 21 days. Chemotherapy dose should be resumed at one dose level below the previous dose or discontinued per investigator's assessment.
Grade 3	• Interrupt ipatasertib (GDC-0068) and chemotherapy treatments until improvement to grade 1 or better. Resume ipatasertib (GDC-0068) and chemotherapy at or one dose level below the previous dose per investigator's assessment. • If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe systemic steroids as clinically indicated. • Perform CT scan and PFTs. Repeat CT scan every four weeks until a return to baseline. Bronchoscopy is recommended. Bronchoscopy is recommended. • For recurrent non-infectious grade 3 pneumonitis events, ipatasertib (GDC-0068) and chemotherapy should be permanently discontinued. • Discontinue ipatasertib (GDC-0068) and chemotherapy if recovery to grade 1 or better is not evident within 21 days.
Grade 4	• Permanently discontinue ipatasertib (GDC-0068) and chemotherapy. • If infectious etiology is ruled out or if improvement is not evident with broad spectrum antibiotics, prescribe systemic steroids as clinically indicated. • Perform CT scan and PFTs. Repeat CT scan every four weeks until a return to baseline. Bronchoscopy is recommended.
CT = computed tomography; PFT = pulmonary function test.	

8.4.6 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. Dose modification guidelines for mucositis attributable to study treatment are outlined in ***Table 16.***

Table 16. Mucositis Management Guidelines.

Severity of Mucositis	Management Guideline
Grade 1 or 2	• Continue study drugs. • Manage with maximum supportive care. • If grade ≥ 2 mucositis recurs in subsequent 4-week cycles, despite maximal supportive care, the dose of ipatasertib (GDC-0068) should be reduced by one dose level. The dose of chemotherapy may be maintained or reduced by one level for subsequent cycles per investigator's discretion.
Grade ≥ 3	• Hold ipatasertib (GDC-0068) and chemotherapy 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. The dose of chemotherapy may be maintained or reduced by one dose level for subsequent cycles per investigator's discretion. • If recovery of mucositis to grade 2 or better does not occur within a maximum of three weeks, the patient will permanently discontinue chemotherapy and ipatasertib (GDC-0068).

8.4.7 Hepatotoxicity

Permanently discontinue ipatasertib for any patients who develop a concurrent elevation of ALT and/or AST greater than 3 × ULN and total bilirubin greater than 2 × ULN and/or clinical jaundice in the absence of biliary obstruction or other causes responsible for the concurrent elevation, including patients having abnormal liver function tests that meet Hy's law criteria. Dosage modification and symptom management guidelines for hepatotoxicity, attributable to study treatment are shown below (see Table 17)

Table 17 Hepatotoxicity Management Guidelines

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

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

8.4.8 Other non-Hematologic Toxicities

If other grade ≥ 3 non-hematologic toxicities not described above develop in patients, treatment with ipatasertib (GDC-0068) and/or chemotherapy regimen 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 (e.g., either ipatasertib [GDC-0068] or chemotherapy agent). Grade ≥ 3 non-hematologic toxicity should be monitored at least weekly.

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

If the toxicity resolves to grade 1 or better after two weeks of treatment interruption, the dose of the attributable drug should be reduced by one level.

Depending on the nature and the severity of the adverse event, if recovery to grade 1 or better takes more than three weeks, the attributable agent may be permanently discontinued, at the discretion of the investigator and after discussion with the Medical Monitor.

8.5 AEs Reporting and Other Safety Related Issues Reporting

For serious and non-serious AEs, the reporting period to the Sponsor (or its designated representative) begins from the time that the patient provides ICF.

Reporting period for SAEs/AESIs that are NOT related with the study IMP and also all non-serious AEs is as follows:

- If patient discontinues treatment during the study, until 30 calendar days after the last administration of the study IMP.
- If patient still on treatment at the time of the EoS visit (See definition on ***Section 4.2.4***) until the EoS visit.

All study patients will be carefully monitored for the occurrence of AEs (including SAEs and AESIs) during the above specified adverse event reporting period.

If the investigator becomes aware of a SAE/AESI at any time after the end of administration of study treatment and believes that it is possibly related to ipatasertib (GDC-0068)/chemotherapy (a serious adverse reaction to ipatasertib [GDC-0068]/chemotherapy), the investigator should notify the serious adverse reaction to the Sponsor immediately irrespective of the time elapsed since last administration of the study IMP.

For all grade ≥ 3 AEs with causal relationship to the IMP, follow-up by the Investigator may be required until the event or its sequelae resolve or stabilize at the level acceptable to the Investigator, and the Sponsor concurs with that assessment.

Clearly related signs, symptoms, and abnormal diagnostic procedure results should be grouped together and reported as a single diagnosis or syndrome whenever possible. Any additional events that fall outside this definition should also be reported separately.

All AEs must be recorded in the CRF.

8.6 SAE reporting and timeframe

Reporting requirements will comply with all EU safety reporting requirements as detailed in Clinical Trials Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, repealing Directive 2001/20/EC and all applicable local regulations for safety reporting.

The investigator or investigator's team will report all protocol defined SAEs and AESIs to the Sponsor (MEDSIR) no later than 24 hours of any site study team staff becoming aware of the event as follows:

- The full details of the SAE and/or AESI should be collected and fully documented using the SAE form and sent to the Sponsor (MEDSIR).
- Follow-up information, copies of any relevant test results, event outcome and the opinion of the investigator as to the relationship between the ipatasertib (GDC-0068)/chemotherapy and the SAE and AESI, accompanied by other applicable documentation when it is requested, will be sent along with the SAE form, if available on the day the event is reported or as soon as possible if it is not.
- The original SAE reporting form and the confirmation from the Sponsor must be kept with the CRF documentation at the study site(s).

All SAE forms will be sent by the investigator or investigator's team to the Sponsor (MEDSIR) according to the reporting instructions provided by MEDSIR at the site initiation visit and filed in the Investigator's File.

SAEs and AESIS will be followed until resolved, a stable outcome is reached, patient is lost to follow-up, or dies.

As sponsor, MEDSIR will be responsible for ensuring that events are reported within the mandated timeframe to the EMA, and other competent authorities, IRBs/ECs, and investigator(s), as necessary and in accordance with all applicable guidelines, approved directives and regulations. All safety reporting local regulatory requirements will be followed.

8.7 Expedited Reporting to Health Authorities, Investigators, IRBs, and ECs

To determine reporting requirements for single SAE cases, MEDSIR (as Sponsor) or its designee, will assess the expectedness of these events using the following reference documents:

- IB for ipatasertib (GDC-0068);
- SmPC for capecitabine;
- SmPC for eribulin;
- SmPC for carboplatin and gemcitabine.

MEDSIR (as Sponsor) or its designee will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Within seven calendar days after being notified of the event, MEDSIR (as Sponsor) or its designee will report unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities, to the investigators and IRBs/ECs. MEDSIR (as Sponsor) or its designee will report other unexpected SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs by a written safety report within 15 calendar days of notification. All safety expedited reports will be reported in accordance to all regulatory reporting obligations (including timelines) and local regulatory requirements.

8.8 Other Safety-Related Reports

As Sponsor, MEDSIR will assess constantly the benefit/risk profile of the trial, that means a continuous evaluation of the safety profile of the drugs under investigation will be done using all available information. MEDSIR will provide the regulatory agencies and competent authorities and the investigators with any relevant information that may affect the benefit/risk profile of the trial. An annual Development Safety Update Report (DSUR) safety report for ipatasertib/chemotherapy will be prepared and distributed by MEDSIR or its designee in accordance to all regulatory reporting obligations and local regulatory requirements.

MEDSIR or its designee will report any finding of noncompliance (as failure to follow any applicable regulation or institutional policies that govern human subjects' research) and/or serious noncompliance (as noncompliance that materially increases risks that result in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants) according to any reporting obligation and local regulatory requirements.

8.9 Pregnancy Reporting

Irrespective of the treatment received by the patient, any patient's or patient's partner pregnancy occurring during study treatment or within 30 days after completing therapy must be reported within 24 hours of investigator's knowledge of the event.

Pregnancies will be treated as SAEs and the investigator will complete a pregnancy form and forward it to the Sponsor according to the reporting instructions provided by MEDSIR at the site initiation visit and filed in the investigator's File.

The patient will be asked to provide follow-up information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriage and congenital abnormalities will also be reported as SAEs.

The follow-up period will be deemed to have ended when the health status of the child has been determined at 12 months of the infant's life.

Additional follow-up information on any ipatasertib/chemotherapy-exposed pregnancy and infant will be requested at specific time points (e.g., after having received the initial report, at the end of the second trimester, two weeks after the expected date of delivery, and at three, six, and 12 months of the infant's life).

Follow-up queries may be sent, asking for further information, if required for a comprehensive assessment of the case.

9 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

9.1 Determination of Sample Size

A total sample of 54 evaluable taxane-pretreated patients (safety run-in phase + non-comparative phase) with unresectable locally advanced or metastatic TNBC will be allocated based on investigator's criteria, in accordance with previous patient's treatments and slots availability, to one of the following treatment arms:

- Arm A: Ipatasertib (GDC-0068) plus capecitabine.
- Arm B: Ipatasertib (GDC-0068) plus eribulin.
- Arm C: Ipatasertib (GDC-0068) and carboplatin plus gemcitabine.

We expected to recruit 18 patients per arm. However, patients could be assigned to one of the other open treatments if one arm was stopped due to feasibility or safety reasons. At the end of the study all 54 patients will be recruited, unless all arms were discontinued.

9.2 Justification of Total Sample Size

This is a pilot study to determine the safety and tolerability of three different study combinations with non-taxane chemotherapy agents and ipatasertib (GDC-0068). The analysis will be exploratory without hypothesis testing. However, The Sponsor has estimated the precision for the incidence of adverse events rate in ipatasertib combinations. Based on Lotus clinical trial (59) the Sponsor assumes a 100% incidence of all grades and 50% grade≥3 adverse events, respectively.

Therefore, a sample size of 18 patients in one arm will provide the following precisions:

- 18.5% to 0% (9.25% half width of confidence interval) assuming an observed AEs

incidence of 100% (i.e. 95% Clopper-Pearson confidence interval of 81.5 to 100%), and

- 24 to 24% (24% half width of confidence interval) assuming an observed AEs incidence of 50% (i.e. 95% Clopper-Pearson confidence interval of 26 to 74%).

9.3 Statistical Plan

No hypothesis testing is planned for this study.

9.4 Analysis Sets

9.4.1 Full Analysis and Safety Analysis Set

All patients who meet selection criteria and receive at least one drug exposure. The full analysis set will be considered the primary population for the analysis.

9.4.2 Safety run-in Set

All patients in safety run-in phase who complete the first two cycles of treatment or who stop treatment during this time because of significant toxicities.

9.4.3 Exploratory Analysis Set

All patients with evaluable samples for biomarker analysis who meet selection criteria and receive at least one drug exposure.

9.5 Safety Analysis (primary objective)

9.5.1 Safety Run-In Analysis

The number and the proportion of patients with significant toxicities in each arm and dosing schedule will be described. The definition of significant toxicities has been presented in ***Section 6.3***. Confidence intervals (CIs) will be calculated, according to Clopper-Pearson (exact binomial intervals). The safety run-in analysis will be developed in safety run-in set.

9.5.2 Analysis of Safety-Related Data

Safety endpoints will be analyzed in full analysis set and separately in the three study arms. We will summarize AEs, AEs grade ≥ 3, SAEs (as described in ***Section 8***), premature withdrawal from study medication, laboratory parameters, exposure to study medication, concomitant medications, vital signs, ECOG performance status, and physical examination.

The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Additional summaries by frequency tables will also be provided for the AEs. Patients who died will be listed together with the cause of death.

Laboratory parameters, hematology and biochemistry, will be presented in shift tables of NCI-CTCAE grade at baseline versus worst grade during treatment.

Other safety variables, such as exposure to study medication, concomitant medications, vital signs, and physical examination, will be analyzed in a similar way. Frequency tables will summarize the exposure of study medication.

ECOG performance status will be summarized over time and the percentage of patients in different categories will be presented by bar charts at different time points.

9.6 Secondary Efficacy Analysis

9.6.1 Response Assessment

The response assessment of the tumor is defined as best response, in terms of complete CR, PR, SD, and progressive disease (PD) according the following list:

- CR: Complete disappearance of all target lesions. Any pathological lymph nodes (target or non-target) must have reduction in short axis to < 10 millimeter (mm).
- PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- SD: Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum diameters while on study. The development of new, previously undetected lesions is also considered progression.

ORR is defined as the number of patients with CR and PR divided by the number of patients in the analysis set. Tumor response will be defined as best response, based on local investigator's assessment according to RECIST criteria guidelines v.1.1.

CBR is defined as the number of patients with CR, PR, or SD (for at least 24 weeks) divided by the number of patients in the analysis set. Tumor response will be defined as best response, based on local investigator's assessment according to RECIST criteria guidelines v.1.1.

9.6.2 Time-to-Event Measures Definitions

- PFS is defined as the period of time from treatment initiation to the first occurrence of disease progression or death from any cause, whichever occurs first, as determined locally by the investigator through the use of RECIST v.1.1. Patients with no progression or no death will be censored at the date of their last evaluable imaging.

- TTR is defined as the time from the treatment initiation to time of the first objective tumor response (tumor shrinkage of ≥ 30%) observed for patients who achieved a CR or PR, as determined locally by the investigator through the use of RECIST v.1.1.
- DoR is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause, whichever occurs first, as determined locally by the investigator through use of RECIST v.1.1. In case of the patient first reaching PR and later CR, the duration of CR will be measured and reported separately, starting from the date when first documented, and ending when a progressive disease is diagnosed, or the patient dies.
- OS is defined as the time from treatment initiation to death from any cause, as determined locally by the investigator through use of RECIST v.1.1. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up. We will analyze 1- and 2-year survival probability. These are defined as the probability of survival at 1 and 2 years after the date of treatment initiation based on the Kaplan-Meier estimate.
- Best percentage of change from baseline in the size of target tumor lesions, defined as the biggest decrease, or smallest increase if no decrease will be observed, as determined locally by the investigator through use of RECIST v.1.1.

9.7 Secondary Efficacy Analysis

All the efficacy analysis will be reported in the full analysis set and separately in the three study arms. The number and proportion of patients with an objective response and CBR with the 95% Pearson-Clopper CI will be calculated.

The best percentage of change from baseline in the size of target tumor lesions will be described with the median, range, mean, standard deviation, and interquartile range. Waterfall plots describing the percentage of change in target tumor lesions according to RECIST v.1.1 criteria will be provided.

Kaplan-Meier plots and swimmer plots for time-to-event endpoints (PFS, TTR, DoR, and OS) will be provided. Finally, number and proportion of events, median survival time, as well as the 1- and 2-year survival rates with corresponding 95% CI, will be calculated.

9.8 Exploratory Endpoints

Biomarkers will be evaluated on a univariate level regarding their potential for prediction of the clinical endpoints (PFS, TTR, ORR, DoR, CBR, OS, and best percentage of change in target tumor lesions). Biomarker and response correlations with clinical covariates will be investigated. It will be checked whether covariates can improve the prediction and whether there is an

interaction with the biomarkers. Relevant covariates could become a part of the statistical prediction model. Further multivariate techniques (e.g., Multiple Logistic Regression, Cox regression, Principal Component Analysis with Rotation, or Cluster Analysis) will be considered in order to study combinations of markers. Techniques to control false discovery rate and overfitting (Lasso, or ridge and elastic net methods) will be adopted. The biomarker analysis will be analyzed in biomarker set.

9.9 Missing Data Management

For PFS, patients without a date of disease progression will be analyzed as censored observations on the date of last tumor assessment. If no post-baseline tumor assessment is available, patients will be censored at the date of treatment initiation + 1 day. Data for patients with an event who missed two or more scheduled assessments immediately prior to the event will be censored at the last tumor assessment prior to the missed visits.

For OS, patients who are not reported as having died will be analyzed as censored observations on the date they were last known to be alive. If no post-baseline data are available, OS will be censored at the date of treatment initiation + 1 day.

For responders and patients with clinical benefit, patients without any post-baseline assessment will be considered as non-responders or without clinical benefit. For the analysis of best percentage of change in tumor lesion we will analyze only observed cases.

9.10 Interim Analysis

The interim analysis will be performed independently in each arm after the last evaluable patient in the run-in phase has completed the two first cycles of study treatment in orden to assess the toxicity profile of each regimen.
The data will be submitted to relevant local health authorities for approval, if/as required, before continuing to Phase IIa stage.
This data will be shared with F. Hoffmann-La Roche Ltd.

9.11 Steering Committee Review

A Steering Committee will be established for this study. It will be composed by the Sponsor's Medical Monitor, Scientific Global Coordinator, Principal investigator/, and additional physicians with experience in experimental therapy management.

During the safety run-in period, the Steering Committee will meet to assess the safety and tolerability of the selected combined treatment regimens used in the study. This meeting will take place after the 3 or 6 first subjects of each Arm have completed the 2 first cycles. This data will be shared with F. Hoffmann-La Roche Ltd.

After this period, data from the interim analysis will be evaluated by the Steering Committee. During this meeting, the decision to continue to Phase IIa or increase the number of patients in the safety run-in phase will be made. The data will be submitted to relevant local health authorities for approval, if/as required, before continuing to Phase IIa stage. This data will be shared with F. Hoffmann-La Roche Ltd.

During phase IIa, the Steering Committee and the study site investigators will meet on demand to review, discuss, and evaluate all of the gathered safety data. In case of any arising safety concern, these meetings can also be called at any time at request of a participating investigator. At these meetings, the Sponsor and the participating investigators must reach a consensus on safety data. The Sponsor will prepare minutes from these meetings and circulate them to each investigator for comments prior to finalization.

Study site investigators and the Sponsor will review patient data at least every six months. Each study site investigator will monitor patient's data for serious toxicities on an ongoing basis.

10 ETHICAL CONSIDERATIONS

10.1 Regulatory and Ethics Compliance

The study will be performed and reported in accordance with the guidelines of the ICH, and the ethical principles laid down in the Declaration of Helsinki. The study will be also compliance with 2001 EU Clinical Trial Directive and any applicable local regulations.

10.2 IRB/EC

Conduct of the study must be approved by an appropriately constituted IRB/EC. Approval is required for the study protocol, protocol amendments, ICFs, study patient information sheets, and advertising materials. The IRB/EC may also be contacted in the event of any major protocol violation (or serious breach if applicable), or any SAE or any urgent safety measures to protect the subjects against any immediate hazard.

The investigator and/or the Sponsor when required, must communicate with the IRB/EC to ensure accurate and timely information is provided at all phases during the study.

The principal investigator, and/or the Sponsor when required, is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments.

In addition to the requirements to report protocol-defined AEs to the Sponsor, investigators are required to promptly report to their respective IRB/EC all unanticipated problems involving risk to human patients. Some IRBs/ECs may want prompt notification of all SAEs, whereas others require notification only about events that are serious, assessed to be related to study treatment, and are unexpected. Investigators may receive written safety reports or other safety-related communications from the Sponsor. Safety reports should be made available to IRB/EC to be reviewed and processed in accordance with regulatory requirements and with the policies and procedures established by their IRB/EC and archived in the site's study file.

10.3 ICF

For each study patient, signed ICF will be obtained prior to any protocol-related activities. As part of this procedure, the study site investigator or designee (if in line with local regulation) must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drugs in such a manner that the study patient is aware of the potential risks, inconveniences, or AEs that may occur. The study patient should be informed that she is free to withdraw from the study at any time and with no obligation to specify her reasons. The patient will receive all information that is required by local regulations and ICH guidelines.

After a failed screening attempt, one re-screening will be allowed to patients who did not meet one or more criteria required for participation in this study. A potential re-screened patient should sign a new ICF before any screening test or study related procedure is performed.

The ICF must be signed and dated by the principal investigator or medical designees (if in line with local regulation) and the patient before any protocol-related activity. The case history or clinical records for each patient shall document the ICF process and that signed ICF was obtained prior to participation in the study.

A copy of each signed ICF must be provided to the patient.

All signed and dated ICFs must remain in each patient's study file and must be available for verification by study monitors at any time.

The ICF should be revised whenever there are changes to procedures outlined in the ICF or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised ICFs, the case history for each patient shall document the ICF process and that written ICF was obtained for the updated/revised ICF for continued participation in the study. The final revised IRB/EC-approved ICF must be provided to the Sponsor for regulatory purposes.

10.4 Data Protection

The Sponsor will ensure the confidentiality of patient's medical information in accordance with all applicable laws and regulations.

The Sponsor as data controller according to the European Directive on the protection of individuals with regard to the processing of personal data and on the free movement of such data (95/46/EC) confirms herewith compliance to Directive 95/46/EC in all stages of data management.

Data generated by this study must be available for inspection upon request by representatives of national and local Health Authorities, the Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

11 SOURCE DOCUMENTATION, STUDY MONITORING, AND QUALITY ASSURANCE

11.1 Source Data Documentation

Source data refers to all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source documents are original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

Sponsor's quality assurance group may assist in assessing whether electronic records generated from computerized medical record systems used at investigational sites can serve as source documents for the purposes of this protocol.

If a site's computerized medical record system is not adequately validated for the purposes of clinical research (as opposed to general clinical practice), applicable hardcopy source documents must be maintained to ensure that critical protocol data entered into the CRFs can be verified.

At a minimum, source documentation must be available to substantiate patient identification, eligibility, and participation; proper ICF procedures; dates of visits; adherence to protocol procedures; adequate reporting and follow-up of AEs; administration of concomitant medication; study drug receipt/dispensing/return records; study drug administration information; and date of completion and reason.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (e.g., all original records, laboratory reports, medical records) in order to ensure data completeness and accuracy as required by study protocol. The investigator and/or site staff must make CRFs and source documents of patients enrolled in this study available for inspection by the Sponsor or its representative at the time of each monitoring visit.

The source documents must also be available for inspection, verification, and copying, as required by regulations, officials of the regulatory Health Authorities (e.g., FDA, EMA, and others), and/or IRBs/ECs. The investigator and study site staff must comply with applicable privacy, data protection, and medical confidentiality laws for use and disclosure of information related to the study and enrolled patients.

The patient must also allow access to the patients' medical records. Each patient should be informed of this requirement prior to the start of the study.

11.2 Study Monitoring and Source Data Verification

Study progress will be monitored by the Sponsor or its representative (e.g., a Clinical Research Organization [CRO]) as frequently as necessary to ensure that:

- The rights and well-being of human patients are protected.
- The reported trial data are accurate, complete, and verifiable from the source documents.
- The conduct of the trial is in compliance with the current approved protocol/amendment(s), Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

Contact details for the team involved in study monitoring will be identified in a hand-out located in the investigator site file.

Data recorded on the CRF will be verified by checking the CRF entries against source documents (e.g., all original records, laboratory reports, medical records, patient diaries) in order to ensure data completeness and accuracy as required by study protocol. The investigator and/or site staff must make CRFs and all source documents of patients enrolled in this study available for monitoring, auditing and/or inspection by the Sponsor/its representative or the regulatory authorities at the time of each monitoring visit, audit and/or inspection.

11.3 Retention of Records

Investigators must retain all study records required by the applicable regulations in a secure and safe facility. The investigator must consult a Sponsor representative before disposal of any study

records and must notify the Sponsor of any change in the location, disposition, or custody of the study files.

Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the IMP. “Essential documents” are defined as documents that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor (ICH E6[R2], 4.9.5). The sponsor should inform the investigator/institution in writing of the need for record retention and should notify the investigator/institution in writing when the trial related records are no longer needed (ICH E6[R2], 5.5.12). However, unless other Union law requires archiving for a longer period, the Sponsor and the Investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. Moreover, the medical files of patients shall be archived in accordance with national law (Article 58 of the European Clinical Trials Regulation [EU] No 536/2014).

The study site investigator must not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The study site investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the Sponsor and the FDA and/or EMA (or respective individual EU country regulatory authorities).

These principles of record retention will also be applied to the storage of laboratory samples, provided that the integrity of the stored sample permits testing.

11.4 Data Quality Assurance

During and/or after completion of the study, quality assurance auditor(s) or inspector(s) named by the Sponsor or by the regulatory authorities may wish to perform on-site audits or inspections. The investigators will be expected to cooperate with any audit or inspection and provide assistance and documentation (including all source data) as requested.

The Sponsor’s representatives are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, monitoring the various records of the clinical study (e.g., CRFs and other pertinent data) provided that patient confidentiality is respected.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with (ICH E6[R2] GCP) and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's (or designee's) quality assurance department. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, (ICH E6[R2] GCP), and applicable country regulatory requirements.

12 DATA MANAGEMENT

12.1 Data Entry and Management

In this study, all data will be entered on to CRFs in a timely manner by the investigator and/or the investigator's dedicated site staff.

The investigator must review data recorded in the CRF to verify their accuracy.

Reconciliation of the data will be performed by the designated CRO. At the conclusion of the study, the occurrence of any protocol violations will be identified and recorded as part of the clinical database. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and will become available for statistical data analysis.

12.2 Data Clarification

As part of the conduct of the trial, the Sponsor may have questions about the data entered by the site, referred to as queries. The monitors and the Sponsor are the only parties that can generate a query.

12.3 Data Coding Procedures

Coding of AEs, medical history, and prior and concomitant medications will be performed using standard dictionaries as described in the data management plan.

13 STUDY MANAGEMENT

13.1 Discontinuation of the Study

The Sponsor reserves the right to discontinue the study for safety or administrative reasons at any time. If the study is discontinued and/or the site is closed for any reason, all investigational

drugs pertaining to the study must be returned to the Sponsor. Any actions required to assess or maintain study patient safety will continue as required, in spite of termination of the study.

13.2 Protocol Amendments

Any change or addition to this protocol requires a written protocol amendment or administrative letter that must be approved by the Sponsor, the scientific global coordinator, the study site investigator, and the IRB/EC before implementation. This requirement for approval should in no way prevent any immediate action from being taken by the study site investigator or the Sponsor in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the study site investigator and is implemented for safety reasons, the Sponsor should be notified as soon as possible (within 24 hours if possible) and the IRB/EC should be informed as necessary.

13.3 Protocol Deviations

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

13.4 Publication Policy Protection of Trade Secrets

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without prior written permission from the scientific global coordinator and the Sponsor. However, authorized regulatory officials, the scientific global coordinator, study site investigators, and the Sponsor (or their representatives) will be allowed full access to inspect and copy the records. All clinical investigational drugs, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by scientific global coordinator or study site investigators and the Sponsor.

The Sponsor will ensure that as far as possible results of this study will be published as scientific/clinical papers in high-quality peer-reviewed journals. Preparation of such manuscripts

will be made with full collaboration of principal investigators and in accordance with the current guidelines of Good Publication Practice.

The Sponsor must be notified of any intent to publish data collected from the study and prior approval from Sponsor must be obtained prior to publication.

14 REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019 Jan;69(1):7–34.

2. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000 Aug 17;406(6797):747–52.

3. Sotiriou C, Pusztai L. Gene-expression signatures in breast cancer. N Engl J Med. 2009 Feb 19;360(8):790–800.

4. Cheang MCU, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009 May 20;101(10):736–50.

5. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clin Cancer Res. 2007 Apr 15;13(8):2329–34.

6. Kreike B, van Kouwenhove M, Horlings H, Weigelt B, Peterse H, Bartelink H, et al. Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res. 2007;9(5):R65.

7. Dent R, Trudeau M, Pritchard KI, Hanna WM, Kahn HK, Sawka CA, et al. Triple-negative breast cancer: clinical features and patterns of recurrence. Clin Cancer Res. 2007 Aug 1;13(15 Pt 1):4429–34.

8. Liedtke C, Mazouni C, Hess KR, André F, Tordai A, Mejia JA, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol. 2008 Mar 10;26(8):1275–81.

9. Hennessy BT, Gonzalez-Angulo A-M, Stemke-Hale K, Gilcrease MZ, Krishnamurthy S, Lee J-S, et al. Characterization of a naturally occurring breast cancer subset enriched in epithelial-to-mesenchymal transition and stem cell characteristics. Cancer Res. 2009 May 15;69(10):4116–24.

10. Prat A, Parker JS, Karginova O, Fan C, Livasy C, Herschkowitz JI, et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. Breast Cancer Research [Internet]. 2010 Sep 2 [cited 2019 Feb 13];12(5):R68. Available from: https://doi.org/10.1186/bcr2635

11. Cheang MCU, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, et al. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clin Cancer Res. 2008 Mar 1;14(5):1368–76.

12. Lehmann BD, Bauer JA, Chen X, Sanders ME, Chakravarthy AB, Shyr Y, et al. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J Clin Invest [Internet]. 2011 Jul 1 [cited 2019 Feb 5];121(7):2750–67. Available from: https://www.jci.org/articles/view/45014

13. Lehmann BD, Pietenpol JA. Identification and use of biomarkers in treatment strategies for triple-negative breast cancer subtypes. J Pathol. 2014 Jan;232(2):142–50.

14. Lehmann BD, Jovanović B, Chen X, Estrada MV, Johnson KN, Shyr Y, et al. Refinement of Triple-Negative Breast Cancer Molecular Subtypes: Implications for Neoadjuvant Chemotherapy Selection. PLoS ONE. 2016;11(6):e0157368.

15. Adams TA, Vail PJ, Ruiz A, Mollaee M, McCue PA, Knudsen ES, et al. Composite analysis of immunological and metabolic markers defines novel subtypes of triple negative breast cancer. Mod Pathol. 2018;31(2):288–98.

16. Masuda H, Baggerly KA, Wang Y, Zhang Y, Gonzalez-Angulo AM, Meric-Bernstam F, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res. 2013 Oct 1;19(19):5533–40.

17. Cortes J, O'Shaughnessy J, Loesch D, Blum JL, Vahdat LT, Petrakova K, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. The Lancet [Internet]. 2011 Mar 12 [cited 2019 Feb 5];377(9769):914–23. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60070-6/abstract

18. Harbeck N, Saupe S, Jäger E, Schmidt M, Kreienberg R, Müller L, et al. A randomized phase III study evaluating pegylated liposomal doxorubicin versus capecitabine as first-line therapy for metastatic breast cancer: results of the PELICAN study. Breast Cancer Res Treat [Internet]. 2017 [cited 2019 Feb 5];161(1):63–72. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5222915/

19. Rugo HS, Roche H, Thomas E, Chung HC, Lerzo GL, Vasyutin I, et al. Efficacy and Safety of Ixabepilone and Capecitabine in Patients With Advanced Triple-negative Breast Cancer: a Pooled Analysis From Two Large Phase III, Randomized Clinical Trials. Clin Breast Cancer. 2018 Dec;18(6):489–97.

20. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med. 1995 Jan;1(1):27–31.

21. Gasparini G, Toi M, Gion M, Verderio P, Dittadi R, Hanatani M, et al. Prognostic significance of vascular endothelial growth factor protein in node-negative breast carcinoma. J Natl Cancer Inst. 1997 Jan 15;89(2):139–47.

22. Gasparini G, Toi M, Miceli R, Vermeulen PB, Dittadi R, Biganzoli E, et al. Clinical relevance of vascular endothelial growth factor and thymidine phosphorylase in patients with node-positive breast cancer treated with either adjuvant chemotherapy or hormone therapy. Cancer J Sci Am. 1999 Apr;5(2):101–11.

23. Linderholm BK, Hellborg H, Johansson U, Elmberger G, Skoog L, Lehtiö J, et al. Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. Ann Oncol. 2009 Oct;20(10):1639–46.

24. Foulkes WD, Stefansson IM, Chappuis PO, Bégin LR, Goffin JR, Wong N, et al. Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst. 2003 Oct 1;95(19):1482–5.

25. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med. 2007 Dec 27;357(26):2666–76.

26. Miles DW, Chan A, Dirix LY, Cortés J, Pivot X, Tomczak P, et al. Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of

human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2010 Jul 10;28(20):3239–47.

27. Robert NJ, Diéras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol. 2011 Apr 1;29(10):1252–60.

28. Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol. 2005 Feb 1;23(4):792–9.

29. O'Shaughnessy JA, Brufsky AM. RiBBON 1 and RiBBON 2: phase III trials of bevacizumab with standard chemotherapy for metastatic breast cancer. Clin Breast Cancer. 2008 Aug;8(4):370–3.

30. Brufsky AM, Hurvitz S, Perez E, Swamy R, Valero V, O'Neill V, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol. 2011 Nov 10;29(32):4286–93.

31. O'Shaughnessy J, Dieras V, Glaspy J, Brufsky A, Miller K, Miles D, et al. Comparison of Subgroup Analyses of PFS from Three Phase III Studies of Bevacizumab in Combination with Chemotherapy in Patients with HER2-Negative Metastatic Breast Cancer (MBC). Cancer Res [Internet]. 2009 Dec 15 [cited 2019 Feb 13];69(24 Supplement):207–207. Available from: http://cancerres.aacrjournals.org/content/69/24_Supplement/207

32. Brufsky A, Rivera RR, Hurvitz SA, Bondarenko IN, Smirnov V, Valero V, et al. Progression-free survival (PFS) in patient subgroups in RIBBON-2, a phase III trial of chemotherapy (chemo) plus or minus bevacizumab (BV) for second-line treatment of HER2-negative, locally recurrent or metastatic breast cancer (MBC). JCO [Internet]. 2010 May 20 [cited 2019 Feb 13];28(15_suppl):1021–1021. Available from: http://ascopubs.org/doi/abs/10.1200/jco.2010.28.15_suppl.1021

33. Gligorov J, Bines J, Alba E, Mustacchi G, Cinieri S, Gupta V, et al. Abstract P2-17-01: Overall survival (OS) in the IMELDA randomized phase III trial of maintenance bevacizumab (BEV) with or without capecitabine (CAP) for HER2-negative metastatic breast cancer (mBC). Cancer Res [Internet]. 2015 May 1 [cited 2019 Feb 13];75(9 Supplement):P2-17-01-P2-17–01. Available from: http://cancerres.aacrjournals.org/content/75/9_Supplement/P2-17-01

34. Robson M, Im S-A, Senkus E, Xu B, Domchek SM, Masuda N, et al. Olaparib for Metastatic Breast Cancer in Patients with a Germline BRCA Mutation. New England Journal of Medicine [Internet]. 2017 Aug 10 [cited 2019 Feb 6];377(6):523–33. Available from: https://doi.org/10.1056/NEJMoa1706450

35. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee K-H, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. New England Journal of Medicine [Internet]. 2018 Aug 23 [cited 2019 Feb 13];379(8):753–63. Available from: https://doi.org/10.1056/NEJMoa1802905

36. Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2018 29;379(22):2108–21.

37. Bardia A, Mayer IA, Diamond JR, Moroose RL, Isakoff SJ, Starodub AN, et al. Efficacy and Safety of Anti-Trop-2 Antibody Drug Conjugate Sacituzumab Govitecan (IMMU-132) in Heavily Pretreated Patients With Metastatic Triple-Negative Breast Cancer. J Clin Oncol. 2017 Jul 1;35(19):2141–8.

38. Starodub AN, Ocean AJ, Shah MA, Guarino MJ, Picozzi, Jr. VJ, Vahdat LT, et al. First-in-Human Trial of a Novel Anti-Trop-2 Antibody-SN-38 Conjugate, Sacituzumab Govitecan, for the Treatment of Diverse Metastatic Solid Tumors. Clin Cancer Res [Internet]. 2015 Sep 1 [cited 2019 Feb 13];21(17):3870–8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4558321/

39. Mina A, Yoder R, Sharma P. Targeting the androgen receptor in triple-negative breast cancer: current perspectives. Onco Targets Ther [Internet]. 2017 Sep 20 [cited 2019 Feb 13];10:4675–85. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5614778/

40. Gucalp A, Tolaney S, Isakoff SJ, Ingle JN, Liu MC, Carey LA, et al. Phase II Trial of Bicalutamide in Patients with Androgen Receptor–Positive, Estrogen Receptor–Negative Metastatic Breast Cancer. Clin Cancer Res [Internet]. 2013 Oct 1 [cited 2019 Feb 13];19(19):5505–12. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4086643/

41. Traina TA, Miller K, Yardley DA, Eakle J, Schwartzberg LS, O'Shaughnessy J, et al. Enzalutamide for the Treatment of Androgen Receptor-Expressing Triple-Negative Breast Cancer. J Clin Oncol. 2018 Mar 20;36(9):884–90.

42. Parker JS, Peterson AC, Tudor IC, Hoffman J, Uppal H. A novel biomarker to predict sensitivity to enzalutamide (ENZA) in TNBC. JCO [Internet]. 2015 May 20 [cited 2019 Feb 13];33(15_suppl):1083–1083. Available from: http://ascopubs.org/doi/abs/10.1200/jco.2015.33.15_suppl.1083

43. Bhaskar PT, Hay N. The two TORCs and Akt. Dev Cell. 2007 Apr;12(4):487–502.

44. Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. Cell. 2007 Jun 29;129(7):1261–74.

45. LoRusso PM. Inhibition of the PI3K/AKT/mTOR Pathway in Solid Tumors. J Clin Oncol. 2016 01;34(31):3803–15.

46. Bellacosa A, Kumar CC, Di Cristofano A, Testa JR. Activation of AKT kinases in cancer: implications for therapeutic targeting. Adv Cancer Res. 2005;94:29–86.

47. Brugge J, Hung M-C, Mills GB. A new mutational AKTivation in the PI3K pathway. Cancer Cell. 2007 Aug;12(2):104–7.

48. Tokunaga E, Oki E, Egashira A, Sadanaga N, Morita M, Kakeji Y, et al. Deregulation of the Akt pathway in human cancer. Curr Cancer Drug Targets. 2008 Feb;8(1):27–36.

49. Clark AS, West K, Streicher S, Dennis PA. Constitutive and inducible Akt activity promotes resistance to chemotherapy, trastuzumab, or tamoxifen in breast cancer cells. Mol Cancer Ther. 2002 Jul;1(9):707–17.

50. Dummler B, Hemmings BA. Physiological roles of PKB/Akt isoforms in development and disease. Biochem Soc Trans. 2007 Apr;35(Pt 2):231–5.

51. Sale EM, Sale GJ. Protein kinase B: signalling roles and therapeutic targeting. Cell Mol Life Sci. 2008 Jan;65(1):113–27.

52. Altomare DA, Testa JR. Perturbations of the AKT signaling pathway in human cancer. Oncogene. 2005 Nov 14;24(50):7455–64.

53. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature. 2012 Oct 4;490(7418):61–70.

54. Millis SZ, Gatalica Z, Winkler J, Vranic S, Kimbrough J, Reddy S, et al. Predictive Biomarker Profiling of > 6000 Breast Cancer Patients Shows Heterogeneity in TNBC, With Treatment Implications. Clin Breast Cancer. 2015 Dec;15(6):473-481.e3.

55. Yang SX, Polley E, Lipkowitz S. New insights on PI3K/AKT pathway alterations and clinical outcomes in breast cancer. Cancer Treat Rev. 2016 Apr;45:87–96.

56. Lin K, Lin J, Wu W-I, Ballard J, Lee BB, Gloor SL, et al. An ATP-site on-off switch that restricts phosphatase accessibility of Akt. Sci Signal. 2012 May 8;5(223):ra37.

57. Lin J, Sampath D, Nannini MA, Lee BB, Degtyarev M, Oeh J, et al. Targeting activated Akt with GDC-0068, a novel selective Akt inhibitor that is efficacious in multiple tumor models. Clin Cancer Res. 2013 Apr 1;19(7):1760–72.

58. Saura C, Roda D, Roselló S, Oliveira M, Macarulla T, Pérez-Fidalgo JA, et al. A First-in-Human Phase I Study of the ATP-Competitive AKT Inhibitor Ipatasertib Demonstrates Robust and Safe Targeting of AKT in Patients with Solid Tumors. Cancer Discov. 2017;7(1):102–13.

59. Isakoff SJ, Saura C, Calvo I, Gil Gil MJ, Patt DA, Morales Murillo S, et al. FAIRLANE: A phase II randomized, double-blind, study of the Akt inhibitor ipatasertib (GDC-0068) in combination with paclitaxel as neoadjuvant treatment for early stage triple-negative breast cancer. JCO [Internet]. 2016 May 20 [cited 2019 Feb 13];34(15_suppl):TPS1105–TPS1105. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.TPS1105

60. Dent R, Im S-A, Espie M, Blau S, Tan AR, Isakoff SJ, et al. Overall survival (OS) update of the double-blind placebo (PBO)-controlled randomized phase 2 LOTUS trial of first-line ipatasertib (IPAT) + paclitaxel (PAC) for locally advanced/metastatic triple-negative breast cancer (mTNBC). JCO [Internet]. 2018 May 20 [cited 2019 Feb 13];36(15_suppl):1008–1008. Available from: http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.1008

61. Oliveira M, Saura C, Calvo I, Andersen J, Coelho JLP, Gil MG, et al. Abstract CT041: Primary results from FAIRLANE (NCT02301988), a double-blind placebo (PBO)-controlled randomized phase II trial of neoadjuvant ipatasertib (IPAT) + paclitaxel (PAC) for early triple-negative breast cancer (eTNBC). Cancer Res [Internet]. 2018 Jul 1 [cited 2019 Feb 13];78(13 Supplement):CT041–CT041. Available from: http://cancerres.aacrjournals.org/content/78/13_Supplement/CT041

62. Kim S-B, Dent R, Im S-A, Espié M, Blau S, Tan AR, et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2017;18(10):1360–72.

63. U.S. Food and Drug Administration. Drug Interactions & Labeling - Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers [Internet]. 2016 [cited 2019 Jan 25]. Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

64. European Medicines Agency. Guideline on the investigation of drug interactions. 2012

Jun;59. Available from: https://www.ema.europa.eu/documents/scientific-guideline/guideline-investigation-drug-interactions_en.pdf

65. Morgillo F, Della Corte CM, Diana A, Mauro C di, Ciaramella V, Barra G, et al. Phosphatidylinositol 3-kinase (PI3Kα)/AKT axis blockade with taselisib or ipatasertib enhances the efficacy of anti-microtubule drugs in human breast cancer cells. Oncotarget. 2017 29;8(44):76479–91.

66. Rajput S, Guo Z, Li S, Ma CX. PI3K inhibition enhances the anti-tumor effect of eribulin in triple negative breast cancer. Oncotarget [Internet]. 2019 Jun 4 [cited 2020 May 11];10(38):3667–80. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6557212/

67. Yoshida T, Ozawa Y, Kimura T, Sato Y, Kuznetsov G, Xu S, et al. Eribulin mesilate suppresses experimental metastasis of breast cancer cells by reversing phenotype from epithelial-mesenchymal transition (EMT) to mesenchymal-epithelial transition (MET) states. Br J Cancer. 2014 Mar 18;110(6):1497–505.

68. Wang X, Wang Y, Gu J, Zhou D, He Z, Wang X, et al. ADAM12-L confers acquired 5-fluorouracil resistance in breast cancer cells. Scientific Reports [Internet]. 2017 Aug 29 [cited 2020 May 11];7(1):9687. Available from: https://www.nature.com/articles/s41598-017-10468-x

69. Gohr K, Hamacher A, Engelke LH, Kassack MU. Inhibition of PI3K/Akt/mTOR overcomes cisplatin resistance in the triple negative breast cancer cell line HCC38. BMC Cancer [Internet]. 2017 Nov 3 [cited 2020 May 11];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5670521/

70. Lin F-M, Yost SE, Wen W, Frankel PH, Schmolze D, Chu P-G, et al. Differential gene expression and AKT targeting in triple negative breast cancer. Oncotarget [Internet]. 2019 Jul 9 [cited 2020 May 11];10(43):4356–68. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6633890/

71. Yang XL, Lin FJ, Guo YJ, Shao ZM, Ou ZL. Gemcitabine resistance in breast cancer cells regulated by PI3K/AKT-mediated cellular proliferation exerts negative feedback via the MEK/MAPK and mTOR pathways. Onco Targets Ther [Internet]. 2014 Jun 13 [cited 2020 May 11];7:1033–42. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4063800/

72. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228–47.

73. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Drug-Induced Liver Injury: Premarketing Clinical Evaluation [Internet]. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2019 [cited 2019 May 10]. Available from: /regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Appendix 1. Schedule of Assessments and Study Procedures

Study Period	**Screening**			**Treatment period***				**Post-Treatment Follow-Up Period**	
Treatment Arm	**Arms A + B + C**			**Arm A**		**Arms B + C**		**Arms A + B + C**	
Day	**-28 to -1**	**-14 to -1**	**-7 to -1**	**Day 1 of each cycle (every 21 days)**	**Cycle 1 day 8**	**Day 1 of each cycle (every 21 days)**	**Day 8 of each cycle[21]**	**Within 30 days after last dose of study treatment (end of treatment)**	**Follow-up every 3 months[20] (survival period)**
Informed Consent Form[1]	X								
Local HR/HER2 status[2]	X								
Baseline signs/symptoms	X								
Check of inclusion/exclusion criteria	X								
Medical history[3]	X								
Complete physical examination and ECOG performance status	X			X		X		X	
Limited physical examination (*diarrhea, nausea, vomiting, mucositis, dyspnea/cough, skin toxicity*)					X		X		
Weight and vital signs[4]	X			X	X	X	X	X	
Body Surface Area (BSA)				X		X			
Concomitant medication reporting[5]	X			X	X	X	X	X	

Review patient diary				X		X			
Study Period	**Screening**			**Treatment period***				**Post-Treatment Follow-Up Period**	
Treatment Arm	**Arms A + B + C**			**Arm A**		**Arms B + C**		**Arms A + B + C**	
Day	**-28 to -1**	**-14 to -1**	**-7 to -1**	**Day 1 of each cycle (every 21 days)**	**Cycle 1 day 8**	**Day 1 of each cycle (every 21 days)**	**Day 8 of each cycle[21]**	**Within 30 days after last dose of study treatment (end of treatment)**	**Follow-up every 3 months[20] (survival period)**
Home glucose monitoring				If clinically indicated					
AE reporting[6]	X			X	X	X	X	X	
Survival status								X	X
Post-study anticancer therapy								X	X
12-lead ECG[7]	X			If clinically indicated					
ECHO or MUGA scan[8]	X			If clinically indicated					
Tumor assessments (chest, abdomen, pelvis)[9]	X			X[9]		X[9]		X[19]	
Bone scans[10]	X[10]			If clinically indicated[10]					
Brain MRI[11]				If clinically indicated[11]					
Tumor samples[12]	X							At the time of progression (if feasible)	
Blood samples[13]	X			X[13]		X[13]		At the time of progression	
	Standard Laboratory Procedures**								
Hematology[14]		X		X		X	X	X[19]	

Fasting Serum Biochemistry[15]		X		X	X	X	X	X[19]	
Study Period	**Screening**			**Treatment period***				**Post-Treatment Follow-Up Period**	
Treatment Arm	**Arms A + B + C**			**Arm A**		**Arms B + C**		**Arms A + B + C**	
Day	**-28 to -1**	**-14 to -1**	**-7 to -1**	**Day 1 of each cycle (every 21 days)**	**Cycle 1 day 8**	**Day 1 of each cycle (every 21 days)**	**Day 8 of each cycle[21]**	**Within 30 days after last dose of study treatment (end of treatment)**	**Follow-up every 3 months[20] (survival period)**
Glycated Hemoglobin HbA1c		X							
INR and PTT (or aPTT)		X							
Pregnancy test[16]			X	X		X		X[19]	
Viral serology[17]	X								
Prophylaxis anti-diarrheal[18]				X[18]		X[18]			
Ipatasertib dispensing and accountability				X		X			
Chemotherapy administration				X		X	X		

Abbreviations: Arm A = Ipatasertib plus capecitabine; Arm B = Ipatasertib and eribulin; Arm C = Ipatasertib plus carboplatin plus gemcitabine.

AE = Adverse events; aPTT = activated partial thromboplastin time; ECG = Electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; HER2 = Human Epidermal Growth Factor Receptor 2; HR = Hormone Receptor; INR = International normalized ratio; MUGA = Multiple-Gated Acquisition; PTT = Partial thromboplastin time.

***** All visits must occur within ± 2 working days (± 1 working day in Day 8 of each cycle). Assessments scheduled for Days 1 and 8 of each cycle must be performed within 48 hours and 24 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up.

** Laboratory tests will be performed at the study site's local laboratory within 48 hours prior to Day 1 of each cycle following ≥ 8-hour fast. Blood test at C1D1 does not need to be repeated if it was performed at screening within 48 hours prior to start of study treatment. For patients included in Arms B or C, laboratory tests will be also performed within 24 hours prior to Day 8 of each cycle.

1. **Informed Consent Form:** Signed written Informed Consent Form obtained prior to any trial-specific procedure.
2. **Local HR/HER2 status:** Confirmation of histological diagnosis and specified estrogen receptor, progesterone receptor, and HER2 status based on local testing on the most recent analyzed biopsy.
3. **Medical history:** Complete medical history and demographics (including age, gender, and ethnic origin). All medications taken in the last 28 days prior to enrolment will be collected.
4. **Weight and vital signs**: Weight, height (only at screening), respiratory rate, blood pressure measurements (systolic and diastolic), pulse rate, and body temperature (oral, axillary, or tympanic temperature).
5. **Concomitant medication reporting:** Relevant concomitant medication will be recorded at screening and on an ongoing basis.
6. **AE reporting:** All Adverse Events occurring during the trial and until 30 days after treatment discontinuation visit (end of treatment visit) have to be recorded with grading according to the NCI-CTCAE v.5.0.
7. **12-lead ECG:** One mandatory ECG at screening. Thereafter, additional ECGs should be performed if clinically indicated (symptoms, use of drugs known to prolong QTc, etc.).
8. **ECHO or MUGA scan:** LVEF assessment must be done within 12 weeks prior to C1D1. Afterwards, cardiac function evaluation should be repeated if clinically indicated.
9. **Tumor assessments (chest, abdomen, pelvis):** Baseline assessments of the chest, abdomen, and pelvis (preferably CT or MRI in case of contrast allergy) must be performed no more than 28 days before the first dose of study treatment. Post-baseline assessments will be performed every 6 weeks (± 3 days)

10. **Bone scans:** Bone imaging is mandatory at baseline and thereafter will be performed every 24 weeks (± 7 days) only for patients with bone lesions identified at baseline, unless clinically or biochemically suspected bone progression. If a bone scan was performed > 28 days but ≤ 60 days prior to start of study treatment, the bone scan does not need to be repeated.
11. **Brain imaging (MRI):** Brain imaging during the trial should be performed only in subjects with known brain metastases (every 6 weeks [± 3 days] for first 6 months and thereafter every 9 weeks [± 7 days]) and those with worsening and/or new neurological symptoms.
12. **Tumor samples:** A tumor tissue sample from a metastatic site or the primary breast tumor must be collected at the time of study entry (mandatory), with the exception of patients for whom tumor biopsies cannot be obtained (e.g., inaccessible tumor or subject safety concern) that may submit an archived metastatic tumor specimen only upon agreement from the Sponsor. If feasible, patients will also be given the option of providing a tumor tissue sample from metastasis or primary breast tumor obtained at disease progression or study termination.
13. **Blood samples:** Blood samples are required for all patients at the time of inclusion, after two cycles of study treatment, and upon progression or study termination.
14. **Hematology:** Hemoglobin, hematocrit, red blood cell count, platelet count, WBC with differential count (ANC, lymphocytes, monocytes, eosinophils and basophils.
15. **Fasting (≥ 8-hour fast) serum biochemistry:** Renal function analysis (serum creatinine, creatinine clearance according to the Cockcroft-Gault formula), liver function [AST, ALT, ALP, gamma-glutamyl transferase (GGT), total and direct bilirubin], amylase, lipase, glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, sodium, potassium, calcium, chloride, magnesium, uric acid, total protein, albumin, and lactate dehydrogenase.
16. **Pregnancy test:** A negative serum pregnancy test must be obtained for women with childbearing potential either within 96 hours prior to C1D1 study treatment administration, or within 7 days of C1D1 (in this case, confirmed by a negative urine pregnancy test prior to C1D1 dosing). In addition, pregnancy tests (serum or urine) are to be performed within 48 hours of Day 1 of each following treatment cycle prior to dosing. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. In case an additional pregnancy test is indicated during the trial, a serum test should be performed.
17. **Viral serology:** Human Immunodeficiency Virus, Hepatitis B surface Antigen (HBsAg), total Hepatitis B core Antibody (HBcAb), Hepatitis C Virus antibody; additional tests for Hepatitis B Virus DNA or Hepatitis C Virus RNA will be required to confirm eligibility.
18. **Prophylaxis anti-diarrheal:** Prophylactic loperamide dose of 2 mg twice a day or 4 mg once a day will be administered daily as prophylaxis for diarrhea during at least the first initial cycle of treatment and may be extended to the next cycle if necessary and if allowed by local guidance. Refer to ***Section 8.4.1*** for further diarrhea management guidance.
19. These assessments do not need to be completed if they have been performed within 1 week before study withdrawal (within 4 weeks for imaging studies).

discontinued treatment for any reason other than progression, tumor assessment will be included in the assessment. EoS will occur at 12 months after the last patient included in the study, unless premature termination of the study.

21. Assessments scheduled for Days 1 and 8 of each cycle, must be performed within 48 hours and 24 hours prior to study treatment administration, respectively, unless otherwise indicated in the schedule of assessments, in order to confirm to the patient if treatment can be followed up. If a mandatory procedure described in the protocol falls on a bank holiday and/or weekend, this procedure should be performed on the day before or after the holiday (e.g., within a period of ± 2 working days). Day 8 visits can be omitted, at the Investigator's discretion, for patients enrolled in Arms B or C that permanently discontinue chemotherapy and continue with ipatasertib (GDC-0068) as single agent. However, laboratory assessments and clinical visits could be scheduled as needed for follow-up of ipatasertib (GDC-0068)-related adverse events. A telephone call may be also acceptable.

Appendix 2. Response Evaluation Criteria In Solid Tumors (RECIST) Guidelines V.1.1.

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.

RECIST v.1.1 (72) will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST v.1.1, CT is the preferred imaging technique in this study.

1. CATEGORIZING LESIONS AT BASELINE

1.1 Measurable lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper (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. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

Note: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

1.2 Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.

· Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

1.3 Normal sites

• Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.

• Normal nodes: Nodes with short axis < 10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease

1.4 Recording tumor assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

1.5 Target lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

• If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

• Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

Note: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

1.6 Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the CRF (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2. OBJECTIVE RESPONSE STATUS AT EACH EVALUATION

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

2.1 Target disease

• Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.

• Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

• Stable disease (SD): Does not qualify for CR, PR or PD. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

• Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

• Indeterminate. Progression has not been documented, and

- one or more target measurable lesions have not been assessed,
- or assessment methods used were inconsistent with those used at baseline,
- or one or more target lesions cannot be measured accurately (e.g., poorly visible unless due to being too small to measure),

- or one or more target lesions were excised or irradiated and have not reappeared or increased.

2.2 Non-target disease

• CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

• Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

• PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

• Indeterminate: Progression has not been determined and one or more non-target sites were not assessed, or assessment methods were inconsistent with those used at baseline.

2.3 New lesions

The appearance of any unequivocal malignant lesion indicated PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

2.4 Supplemental investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion ay be investigated with biopsy or fine needle aspirate to clarify status.

2.5 Subjective progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Table 18. Objective Response Status at Each Evaluation.

Target Lesions	Non-Target Disease	New Lesions	Objective Status
CR	CR	No	**CR**
CR	Non-CR/Non-PD	No	**PR**
CR	Indeterminate or Missing	No	**PR**
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	**PR**
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	**Stable**
Indeterminate or Missing	Non-PD	No	**Indeterminate**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Table 19. Objective Response Status at Each Evaluation for Patients with Non-Target Disease Only.

Non-Target Disease	New Lesions	Objective Status
CR	No	**CR**
Non-CR/Non-PD	No	**Non-CR/Non-PD**
Indeterminate	No	**Indeterminate**
Unequivocal progression	Yes or No	**PD**
Any	Yes	**PD**

Appendix 3. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law.

1. INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law (HL). It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates in reviewing and assessing of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the IMP.

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AE and SAE according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

2.1 Potential Hy's Law (PHL)

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

2.2 Hy's Law (HL)

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

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

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

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

Note: There are different processes for the identification of potential Hy's law cases depending on whether central or local laboratories are being used.

When a patient meets any of the identification criteria, in isolation or in combination, the Investigator will immediately:

- Notify the Sponsor's representative (or designee's);
- Request a repeat of the test (new blood draw) by the local laboratory;
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.

When the identification criteria are met from local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see ***2. Definition*** within this **Appendix**) by reviewing laboratory reports from all previous visits.

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor's representative (or designee's);
- Promptly enter the laboratory data into the laboratory CRF.

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria Not Met

If the patient does not meet PHL criteria the Investigator will:

- Inform the Sponsor's representative (or designee's) that the patient has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria Met

If the patient does meet PHL criteria the Investigator will notify the Sponsor's representative (or designee's).

The Sponsor's Medical Scientist contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated;
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Sponsor's Medical Scientist;
- Complete the Liver CRF Modules as information becomes available
- If at any time (in consultation with the Sponsor's Medical Scientist) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

4.3 Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Sponsor's Medical Scientist contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP.

The Scientific Global Coordinator and Principal Investigator will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF;

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the Sponsor's standard processes.

If it is agreed that there is NO explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to Sponsor's standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply;
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above;
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

4.4 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study?

If No, follow the process described in

***Potential Hy's Law Criteria* Met** of this Appendix.

If Yes, determine if there has been a significant change in the patient's condition [1] compared with when PHL criteria were previously met:

- If there is no significant change no action is required;
- If there is a significant change, it is critical to initiate close observation immediately in order to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress:
  - Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic. - Obtaining a more detailed history of symptoms and prior or concurrent diseases;
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets;
  - Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease;
  - Obtaining a history of exposure to environmental chemical agents;
  - Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin);
  - Considering gastroenterology or hepatology consultations.

Discontinuation of treatment should be considered if:

- ALT or AST >8xULN;
- ALT or AST >5xULN for more than 2 weeks;
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5);
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

[1] *Note: A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Sponsor's Medical Scientist if there is any uncertainty.*

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation' (73):

https://www.fda.gov/media/116737/download