RESEARCH PROTOCOL

PILOT CLINICAL TRIAL OF TREATMENT WITH LY3023414 AND PREXASERTIB TO INHIBIT HOMOLOGOUS RECOMBINATION (HR) IN PATIENTS WITH CHEMOTHERAPY-PRETREATED METASTATIC TRIPLE NEGATIVE BREAST CANCER

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SITE INVESTIGATOR SIGNATURE PAGE

The signature below constitutes the approval of this protocol entitled "Pilot clinical trial of treatment with LY3023414 and prexasertib to inhibit homologous recombination (HR) in patients with chemotherapy-pretreated metastatic triple negative breast cancer", and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Site Investigator:

Signed: _____ Date: _____

Name:_____

ABBREVIATIONS

Abbreviation	Term
5-FU	5-fluorouracil
AE	Adverse event
AKT	Protein kinase B
ALT	Alanine aminotranserase
ANC	Absolute neutrophil count
ASCO	American society of clinical oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BC	Breast cancer
BID	bis in die; twice a day
BRCA	Breast cancer susceptibility gene
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CHK1	Checkpoint kinase 1
CI	Confidence interval
CL	Drug clearance
Cmax	Maximum (or peak) serum concentration
CMP	Complete metabolic profile
CO_2	Carbon dioxide
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTEP	Cancer Therapy Evaluation Program
CR	Complete response
CRF	Case report form
CV	Coefficient of variation
CYP	Cytochrome P450
DLCO	Diffusing capacity
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen receptor
FDA	Food and Drug Administration
FEC/T	5-fluorouracil, epirubicin, cyclophosphamide plus docetaxel
FFPE	Formalin-fixed paraffin embedded

G-CSF	Granulocyte colony stimulating factor
gm	Gram
HbA1c	Hemoglobin A1c
HER2	human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act of 1996
HR	Homologous recombination
hr	Hour
HRD	Homologous recombination deficiency
IC_{50}	Concentration of an inhibitor where the response (or binding) is reduced by half
ID	Identification
IM	Internal mammary
IRB	Institutional Review Board
ITT	Intent to treat
IV	Intravenous
JAK	Janus kinase
L	Liter
LFU	Lost to follow up
LN	Lymph node
m	Meter
MAPK	Map kinase
Mg	Magnesium
mg	Milligram
mm	Millimeter
MBC	Metastatic breast cancer
metTNBC	Metastatic TNBC
mg	Milligram
mL	Milliliter
mOsm	Milliosmole; 1/1,000 of an osmole
MRI	Magnetic resonance imaging
ms	Millisecond
mTOR	mechanistic target of rapamycin
mTOR[1] or [2]	target of rapamycin complex [1 or 2]
ng	Nanogram
NGS	Next generation sequencing
NHEJ	Non-homologous end-joining
NSCLC	Non-small cell lung cancer
PARP	Poly (ADP-ribose) polymerase
P	Phosphorus
PI	Principal Investigator
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase

PD	Progressive Disease or Pharmacodynamics
PgR	Progesterone receptor
PK	Pharmacokinetics
PO	per os; by mouth (orally)
PR	Partial response
PS	Performance scale
QD	quaque die; each day; once daily
QT	Measure between Q wave and T wave in the heart's electrical cycle
QTcF	QT corrected for HR using Fridericia's method
RPPA	Reverse phase protein array
SAE	Serious adverse event
SC	Supraclavicular
SCLC	Small cell lung cancer
SD	Stable disease
SOP	Standard operating procedure
STAT	Signal transducer and activator of transcription
TEAE	Treatment-emergent adverse events
TK	Toxicokinetics
TNBC	Triple negative breast cancer
ULN	Upper limits of normal
Vss	Volume of distribution at steady-state
WLN	Within normal limits

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SYNOPSIS

Summary:

Seventy to 80% of breast cancers have a basal gene expression profile which is characterized by homologous recombination deficiency (HRD) and high proliferation. HRD leads to upregulation of the activity of the non-homologous end joining (NHEJ) error-prone pathway that repairs DNA double strand breaks, a process required for TNBC survival. The hypothesis of this pilot trial is that administration of LY3023414 and prexasertib will inhibit NHEJ in metastatic TNBC. A patient with an exceptional complete and durable response of her primary-refractory metastatic TNBC with PI3K pathway inhibition followed at disease progression by nab paclitaxel/cisplatin provides the clinical rationale for the present trial which will utilize LY3023414 and prexasertib to inhibit HR proficiency in pretreated metastatic TNBC patients.

Patients will be treated with 150 mg LY3023414 PO BID and prexasertib 80 mg/m^2 IV administered every 2 weeks until disease progression or unacceptable toxicity. Metastatic TNBC patients will undergo core needle biopsies of a metastatic lesion at study entry, and any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted. Treatment will be discontinued in patients who achieve a confirmed clinical complete response, and these patients will be followed to document the durability of the complete responses.

Patients whose disease does not respond to prexasertib may be treated with standard of care breast cancer therapies **off study**, at the recommendation of the treating physician.

Objectives:

The primary objective of this study is to assess the objective response rate (CR+PR) associated with LY3023414 and prexasertib in metastatic TNBC patients.

The secondary objectives of this protocol are:

1. To assess the duration of response to combination treatment with LY3023414 and prexasertib in metTNBC pts.
2. To assess the serial metastatic TNBC biopsy for homologous recombination deficiency (HRD) by evaluating inactivating mutations in HR genes on Next Generation Sequencing (NGS), by evaluating the overall and pattern-specific mutational load in the cancers on NGS, and by assessing H2AX expression by RPPA.
3. To assess expression of phosphorylated nuclear EGFR, AKT, DNA-PK and other proteins involved in HR as well as activation of the PI3K, MAPK and JAK/STAT pathways in baseline metTNBC tissues on reverse phase protein arrays (RPPA) as possible predictors of clinical antitumor response to LY3023414 and prexasertib.

Number of patients: 10

Inclusion Criteria:

A patient will be considered for enrollment in this study if all the following criteria are met:

1. Patients ≥18 years of age. Patients must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception during treatment with study drug and for at least 12 weeks following the last dose of study drug.
2. Have a diagnosis of metastatic TNBC previously treated with standard anthracycline, cyclophosphamide, and taxane chemotherapy, unless there was a contraindication to doxorubicin, in which case prior treatment with this agent is not required. **NOTE:** TNBC defined as ER-negative tumors with ≤10% tumor nuclei immunoreactivity, or "ER Low Positive" as defined by the updated ASCO/CAP guidelines 2020.
3. Have not received more than 3 prior chemotherapy regimens for metastatic disease. Prior platinum and/or taxane therapy in the adjuvant or metastatic setting is permitted.
4. Have locoregional (eg, breast, chest wall, regional lymphatic) or pulmonary or hepatic metastatic disease that is amenable to core needle biopsy. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted. If a skin biopsy cannot be safely obtained, patients may still be eligible, per physician discretion.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (See Appendix I)
6. Have adequate hematologic function, defined by:
    a. Absolute neutrophil count (ANC) >1500/mm^3
    b. Platelet count ≥100,000/mm^3
    c. Hemoglobin ≥9 g/dL
7. Have adequate liver function, defined by:
    a. AST and ALT ≤2.5 x the upper limit of normal (ULN) or ≤5 x ULN in presence of liver metastases
    b. Total bilirubin ≤1.5 x ULN
8. Have adequate renal function, defined by:
    a. Serum creatinine ≤1.5 x ULN or calculated creatinine clearance of ≥60 ml/min
9. Have the ability to swallow oral medications
10. Patients who have a history of brain metastasis are eligible for the study provided that all the following criteria are met:
    a. Brain metastases which have been treated
    b. Off-treatment with steroids for 2 weeks before administration of the first doses of LY3023414 and prexasertib
    c. No ongoing requirement for dexamethasone or anti-epileptic drugs
    d. No clinical or radiological evidence of progression of brain metastases
11. Patient must be accessible for treatment and follow-up.
12. All patients must be able to understand the investigational nature of the study and give written informed consent prior to study entry.

Exclusion Criteria:

A patient will be ineligible for inclusion in this study any of the following criteria are met:

1. Have a family history of long QT Syndrome and serious cardiac conditions.
2. Have QTcF interval of >470 msec on screening electrocardiogram (ECG) as well as on pre-dose Cycle 1 Day 1 ECG
3. Have insulin-dependent diabetes mellitus. Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c <8%. Patients with type 1 diabetes mellitus are not eligible.
4. Previous radiotherapy for metastatic disease completed <2 weeks prior to study treatment initiation.
5. Women who are pregnant or lactating.
6. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation such as:
    a. severe impaired lung functions as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O_2 saturation that is 88% or less at rest on room air
    b. liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
    c. viral hepatitis or HIV.
7. Concurrent use of CYP3A4 inhibitors and inducers from 72 hours prior to initiation of study treatment until the end of treatment.
8. History of any other disease, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug, or that might affect interpretation of the results of this study, or render the patient at high risk for treatment complications.
9. Patients who have received prior PI3K or CHK therapy.
10. Any other investigational or anti-cancer treatments while participating in this study
11. Any other active malignancy.

Medication and Doses:	This exploratory open label pilot trial will evaluate the administration of LY3023414 and prexasertib in patients with metastatic TNBC. Metastatic TNBC patients will consent to and undergo core needle biopsies of a metastatic lesion for NGS, RPPA and other molecular analyses at study entry. Patients will then be treated with 150 mg LY3023414 PO BID and prexasertib 80 mg/m^2 IV administered every 2 weeks until disease progression or unacceptable toxicity. Any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion, a second core needle biopsy of the same metastatic lesion (or different metastases if the initial metastasis has regressed) will be performed for RPPA and other molecular analyses. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted. Treatment will be discontinued in patients who achieve a confirmed clinical complete response, and these patients will be followed to document the durability of the complete responses.

	Patients whose disease does not respond to the combination of LY3023414 and prexasertib may be treated with standard of care breast cancer therapies **off study**, at the recommendation of the treating physician.
Duration of Study:	The duration of patient participation in the study will be a maximum of 18 months.

Efficacy Assessments:	**Safety Assessments:**
CR, PR, SD, PD	Toxicity

PART I – CLINICAL TRIAL PROTOCOL

1 INTRODUCTION

1.1 BACKGROUND ON TRIPLE NEGATIVE BREAST CANCER

Breast cancer is the most common malignancy in women worldwide, with incidence rates as high as 89.7 per 100,000 women.[1] Although there have been a number of important treatment advances in recent years, and overall mortality is declining due to earlier detection and more effective treatment of early stage disease, metastatic breast cancer (MBC) remains incurable and is the second leading cause of cancer deaths among women.[2]

Triple-negative breast cancer (TNBC) is defined by the absence of ER, PgR, and HER2 receptor expression. By hierarchical clustering of gene expression patterns, these cancers most often segregate with the "basal-like" intrinsic subtype.[3] Compared with other breast cancer subtypes, TNBC is associated with a worse prognosis, including a shorter time to recurrence in early-stage disease, and a shorter time between recurrence and death in the metastatic setting.[4] Because currently available targeted therapies such as endocrine or HER2-targeted agents are ineffective against this breast cancer subtype, treatment options for TNBC are limited to chemotherapy at this time. To date, no clear molecular target has been identified and proven to have therapeutic value.

1.2 HOMOLOGOUS RECOMBINATION DEFICIENCY IN BREAST CANCER

Seventy to 80% of breast cancers have a basal gene expression profile which is characterized by homologous recombination deficiency (HRD) and high proliferation.[5] HRD leads to upregulation of the activity of the non-homologous end joining (NHEJ) error-prone pathway that repairs DNA double strand breaks, a process required for TNBC survival.[6] A key nuclear enzyme that orchestrates NHEJ is DNA-Dependent Protein Kinase catalytic subunit (DNA-PKcs), a member of the PI3K super-family.[7]

Nuclear Epidermal Growth Factor Receptor (EGFR) is activated by phospho-AKT and both nuclear EGFR and nuclear AKT phosphorylate and activate DNA-PK to promote NHEJ-mediated repair of DNA double-strand breaks.[8] Loss of HR proficiency, which occurs in most TNBCs (the basal-like TNBCs), leads to increased EGFR expression in mammary epithelial cells.[9] However, it is not known whether activated, nuclear EGFR T564 and nuclear AKT that phosphorylate DNA-PK are increased in the setting of HRD in chemotherapy-resistant TNBC.

BEZ-235 is a potent inhibitor of DNA-PKcs, as well as PI3K and TORC1/2, which inhibits NHEJ-mediated DNA double strand break repair, sensitizing cancers to DNA damaging agents.[10] A phase I trials of the sachet formulation of BEZ-235 demonstrated that BEZ-235 was safe with manageable toxicities(including mild to moderate fatigue, nausea, diarrhea, hyperglycemia, stomatitis and anemia) and had demonstrated antitumor activity against breast cancer.[11] However, although the mechanisms behind its activity were compelling, clinical development of this agent was stopped because of highly unpredictable intrapatient bioavailability that could not be overcome with various formulations (Novartis Oncology, personal communication, October, 2015).

Another mechanism which inhibits DNA repair response is the dual inhibition of mTORC1/2. In preclinical studies, the dual inhibition of mTORC1 and mTORC2 decreased DNA repair response as well as decreased the activity of AKT. This dual inhibition allowed for the partial re-sensitization of platinum-resistant ovarian cancer cells both in vitro and in vivo to platinum chemotherapy, as compared to single inhibition of mTORC1.[12] Blockade of the mTOR complexes may be a novel strategy to sensitize cancers to DNA damaging agents.

1.3 LY3023414

The phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway has been reported as activated in >70% of human cancers and has emerged as a promising target for anticancer therapies. PI3K/mTOR signaling plays a central role in regulating physiological processes such as growth, survival, proliferation, and metabolism as well as in the development of malignant disease.[13] Aberrations in PI3K/mTOR signaling by various mechanisms have been described, which lead to increased tumor proliferation, inhibition of apoptosis, and angiogenesis in preclinical models. In cancer patients, genes involved in signal transduction through the PI3K/mTOR pathway may harbor mutations more commonly than any other pathway regulating cell growth and survival. Such mutations are reported to occur in breast, colon, ovarian, gastric, prostate, mesothelioma, endometrial, brain, and lung cancers.[13]

LY3023414 is an oral PI3K/mTOR inhibitor which selectively inhibits class I PI3K isoforms, mTOR, and DNA-PK via an ATP-competitive mechanism of action.[14] In vitro, LY3023414 demonstrated a cytostatic antiprofilerative effect, with cells accumulating in G1; no induction of apoptosis was observed. Strong pathway inhibition (ie, dephosphorylation of PI3K/AKT/mTOR pathway downstream substrates [AKT, S6K, S6RP, and 4EBP1]) was observed. Dose-responsive inhibition of tumor growth was observed in preclinical xenograft models when LY3023414 was administered as a single agent, in addition to synergistic antiproliferative effects when LY3023414 was combined with standard of care agents.[14]

The first-in-human study of LY3023414 is a phase 1 trial that was conducted in adult patients with advanced solid tumors refractory to standard therapies.[15] As of September 2014 (reported at ASCO 2015), a total of 47 patients had received LY3023414 either QD or BID. Common treatment-related adverse events (all grades) included nausea (38%), fatigue (31%), vomiting (27%), and diarrhea (17%). A durable partial response was observed in one patient with endometrial cancer which harbored both PIK3R1 and PTEN mutations, and 22 additional patients (47%) had stable disease as their best response. LY3023414 is currently being studied in tumor-specific expansion cohorts for mesothelioma, breast cancer, indolent Non-Hodgkin Lymphoma and squamous NSCLC. LY3023414 appears to be safe when administered as single agent up to 325 mg QD or 200 mg BID. The recommended phase 2 dose for single-agent LY3023414 is 200 mg PO BID, based on safety, tolerability, PK/PD, and preliminary antitumor activity.[15]

1.4 PREXASERTIB (FORMERLY LY2606368)

CHK1 is a serine threonine protein kinase that is required for checkpoint-mediated cell cycle arrest to allow for the activation of DNA repair, once DNA damage has been detected.[16,17] Preclinical studies in triple negative breast cancer[17] and head and neck cancer[18] have demonstrated that CHK1 inhibitors can augment the cytotoxic effects of DNA-damaging

treatments. The loss of CHK1 leads to HRD and therefore to a strong dependence on NHEJ, and the dual inhibition of CHK1 and NHEJ would create a synthetically lethal event.[19] In addition, cell lines deficient in the Fanconi anemia DNA repair pathway (homologous recombination) have been shown to be hypersensitive to CHK1 inhibition, such that inhibiting CHK1 is synthetically lethal to these cells.[20]

Prexasertib (previously LY2606368) is an ATP-competitive protein kinase inhibitor that showed selectivity to CHK1. Preclinical studies in SCLC[16] demonstrated that prexasertib had notable single-agent activity, enhanced cisplatin cytotoxicity in platinum-resistant models, and when combined with the PARP inhibitor olaparib, caused tumor regression and increased survival. Prexasertib recently completed phase I testing, which demonstrated tolerability as well as single-agent clinical activity in a subset of solid tumors.[16] In a single arm, phase II pilot trial in BRCA wild type triple negative breast cancer patients, prexasertib exhibited modest single agent activity, warranting further evaluation as part of combination therapy.[21]

A recent study of single-agent prexasertib in recurrent high-grade serous or high-grade endometrioid ovarian carcinoma demonstrated tolerability and clinical activity.[22] Twenty-eight women were enrolled in the study and received at least 1 dose of prexasertib; 79% of patients had disease that was platinum-resistant or platinum-refractory. Of the 28 patients, 24 were assessable per protocol and RECIST response. Eight (33%) of 24 patients had partial responses, which were identified during the first tumor reassessment (in the intent-to-treat population, 8 [29%] patients of 28 had partial response). Median progression-free survival was 7.4 months in the 24 assessable patients, and the most commonly reported adverse event was neutropenia in 26 (93%) of 28 patients. This proof-of-concept, phase 2 prexasertib study in ovarian cancer with encouraging findings warrants further development and validation.[22]

1.5 LY3023414 AND PREXASERTIB IN COMBINATION

Dual inhibition of the CHK1 and PI3K/mTOR signaling pathways may disrupt homologous recombination repair. In prexasertib-resistant TNBC PDX models, the PI3K/AKT signaling pathway is transcriptionally elevated. In a nonclinical model, synergistic antitumor activity was observed when prexasertib was combined with a PIK3K/mTOR inhibitor.[23]

In a Phase 1b dose-escalation study, LY3023414 and prexasertib were given simultaneously in patients with advanced and/or metastatic cancer. Pharmacokinetic properties for each co-administered agent were consistent with monotherapy PK profiles. Doses recommended for LY3023414 is 150 mg BID, while prexasertib recommended dose is 105 mg/m^2. The most common adverse events were neutropenia, thrombocytopenia, anemia, nausea, and fatigue. These toxicities were consistent with the respective monotherapy profiles, although the incidence was higher. Supportive care may be required. The combination showed preliminary efficacy in solid tumors; in TNBC, 25% of patients had a partial response, and 37.5% had stable disease.[23]

1.6 EXCEPTIONAL RESPONDER CLINICAL HISTORY AND TUMOR MOLECULAR ALTERATIONS

The clinical and molecular tumor characteristics of a metastatic TNBC exceptional responder patient to sequential treatment with BEZ-235 followed by cisplatin and nab paclitaxel provides the clinical rationale for conducting the proposed prospective pilot clinical trial of LY3023414 and prexasertib.[24] Briefly, after several recurrences and treatments, the patient developed a durable complete response (CR) after BEZ-235 therapy followed by nab paclitaxel plus cisplatin

that has been **ongoing for almost 5 years**. All the patient's serial BC specimens revealed a conversion from proficient homologous recombination to deficient homologous recombination, measured via several molecular analyses.

Dual inhibition of CHK1 and PI3K/mTOR may disrupt homologous recombination repair, and the combination of LY3023414 and prexasertib has shown preliminary efficacy in a Phase 1b study.

1.7 RATIONALE

The hypothesis of this pilot trial is that administration of LY3023414 and prexasertib will inhibit NHEJ in metastatic TNBC. The exceptional responder patient's treatment history described in the Introduction provides the clinical rationale for the present trial which will utilize LY3023414 and prexasertib to inhibit HR proficiency. The trial will include in depth analysis of the patients' TNBC genome and phosphoproteome to evaluate HR-proficiency and deficiency, and nuclear proteins that drive NHEJ: at baseline and any time after completion of Cycle 2 of the treatment combination, or at the physician's discretion.

2 TRIAL OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objective of this study is to assess the objective response rate (CR+PR) associated with LY3023414 and prexasertib in metastatic TNBC patients.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this protocol are:

1. To assess the duration of response to combination treatment with LY3023414 and prexasertib in metTNBC pts.
2. To assess the serial metastatic TNBC biopsy for homologous recombination deficiency (HRD) by evaluating inactivating mutations in HR genes on Next Generation Sequencing (NGS), by evaluating the overall and pattern-specific mutational load in the cancers on NGS, and by assessing H2AX expression by RPPA.
3. To assess expression of phosphorylated nuclear EGFR, AKT, DNA-PK and other proteins involved in HR as well as activation of the PI3K, MAPK and JAK/STAT pathways in baseline metTNBC tissues on reverse phase protein arrays (RPPA) as possible predictors of clinical antitumor response to LY3023414 and prexasertib.

3 STUDY DESIGN

This exploratory open label pilot trial will evaluate the administration of LY3023414 and prexasertib in patients with metastatic TNBC.

Metastatic TNBC patients will consent to and undergo core needle biopsies of a metastatic lesion for NGS, RPPA, and other molecular analyses at study entry.

Patients will then be treated with 150 mg LY3023414 PO BID and prexasertib 80 mg/m^2 IV administered every 2 weeks until disease progression or unacceptable toxicity. Any time after the

completion of Cycle 2 of the treatment combination, or at the physician's discretion, a second core needle biopsy of the same metastatic lesion (or different metastases if the initial metastasis has regressed) will be performed for RPPA and other molecular analyses. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.

Treatment will be discontinued in patients who achieve a confirmed clinical complete response, and these patients will be followed to document the durability of the complete responses.

Patients whose disease does not respond to the combination of LY302314 and prexasertib may be treated with standard of care breast cancer therapies **off study**, at the recommendation of the treating physician.

4 SELECTION OF PATIENTS

4.1 SAMPLE SIZE

Ten patients with metastatic TNBC will be enrolled over 12-18 months.

4.2 INCLUSION CRITERIA

A patient will be eligible for inclusion in this study if **he or she** meets **all** of the following criteria:

1. Patients ≥18 years of age. Patients must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception during treatment with study drug and for at least 12 weeks following the last dose of study drug.
2. Have a diagnosis of metastatic TNBC previously treated with standard anthracycline, cyclophosphamide, and taxane chemotherapy, unless there was a contraindication to doxorubicin, in which case prior treatment with this agent is not required. **NOTE:** TNBC defined as ER-negative tumors with ≤10% tumor nuclei immunoreactivity, or "ER Low Positive" as defined by the updated ASCO/CAP guidelines 2020.[25]
3. Have not received more than 3 prior chemotherapy regimens for metastatic disease. Prior platinum and/or taxane therapy in the adjuvant or metastatic setting is permitted.
4. Have locoregional (eg, breast, chest wall, regional lymphatic) or pulmonary or hepatic metastatic disease that is amenable to core needle biopsy. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted. If a skin biopsy cannot be safely obtained, patients may still be eligible, per physician discretion.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (See Appendix I)
6. Have adequate hematologic function, defined by:
    a. Absolute neutrophil count (ANC) >1500/mm^3
    b. Platelet count ≥100,000/mm^3
    c. Hemoglobin ≥9 g/dL
7. Have adequate liver function, defined by:
    a. AST and ALT ≤2.5 x the upper limit of normal (ULN) or ≤5 x ULN in presence of liver metastases

b. Total bilirubin ≤1.5 x ULN

8. Have adequate renal function, defined by:
    a. Serum creatinine ≤1.5 x ULN or calculated creatinine clearance of ≥60 ml/min
9. Have the ability to swallow oral medications
10. Patients who have a history of brain metastasis are eligible for the study provided that all the following criteria are met:
    a. Brain metastases which have been treated
    b. Off-treatment with steroids for 2 weeks before administration of the first doses of LY3023414 and prexasertib
    c. No ongoing requirement for dexamethasone or anti-epileptic drugs
    d. No clinical or radiological evidence of progression of brain metastases
11. Patient must be accessible for treatment and follow-up.
12. All patients must be able to understand the investigational nature of the study and give written informed consent prior to study entry.

4.3 EXCLUSION CRITERIA

A patient will be ineligible for inclusion in this study if **he or she** meets **any** of the following criteria:

1. Have a family history of long QT Syndrome and serious cardiac conditions.
2. Have QTcF interval of >470 msec on screening electrocardiogram (ECG) as well as on pre-dose Cycle 1 Day 1 ECG.
3. Have insulin-dependent diabetes mellitus. Patients with a type 2 diabetes mellitus are eligible if adequate control of blood glucose level is obtained by oral anti-diabetics as documented by HbA1c <8%. Patients with type 1 diabetes mellitus are not eligible.
4. Previous radiotherapy for metastatic disease completed <2 weeks prior to study treatment initiation.
5. Women who are pregnant or lactating.
6. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation such as:
    a. severe impaired lung functions as defined as spirometry and DLCO that is 50% of the normal predicted value and/or O_2 saturation that is 88% or less at rest on room air
    b. liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C).
    c. viral hepatitis or HIV.
7. Concurrent use of CYP3A4 inhibitors and inducers from 72 hours prior to initiation of study treatment until the end of treatment.
8. History of any other disease, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates use of an investigational drug, or that might affect interpretation of the results of this study, or render the patient at high risk for treatment complications.
9. Patients who have received prior PI3K or CHK therapy.

10. Any other investigational or anti-cancer treatments while participating in this study
11. Any other active malignancy

4.4 REASONS OFF TREATMENT

Patients will be taken off treatment if any of the following occur (off treatment assessments should be completed within 30 days ± 2 days; please refer to Section 8.3):

1. Disease progression on treatment
2. Intolerable toxicity
3. Treatment (either one or both therapies) is interrupted for more than 3 weeks for any reason.
4. An intercurrent illness, which would in the judgment of the Investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment
5. Non-protocol therapy (chemotherapy, radiotherapy, hormonal therapy, immunotherapy, or surgery) is administered during study treatment
6. Noncompliance with protocol or treatment
7. Becomes pregnant
8. Refuses to continue treatment (patient will continue to be followed for survival)
9. Completion of treatment portion of the protocol
10. Patients who achieve a confirmed clinical complete response
11. Physician decision

The date of and reason for discontinuation must be noted on the Change of Status page of the Case Report Form (CRF). Every effort should be made to complete the appropriate assessments.

4.5 REASONS OFF STUDY

Patients will be considered off study if any of the following occur:

1. Withdrawal of consent (patient will not be contacted and no further information will be collected). All data collected prior to withdrawal of consent may be used in the data analysis.
2. Termination of study by Baylor IRB, Eli Lilly and Company, or Principal Investigators
3. Lost to follow-up (3 attempts should be documented in the patient's source document before the site considers the patient as LFU)
4. Death

The date of and reason for discontinuation must be noted on the Case Report Form (CRF). Every effort should be made to complete the appropriate assessments.

If the patient is withdrawn for any reason, the end of study assessments must be completed. Patients who withdraw from the study treatment due to intolerable toxicity will still be followed for outcome and toxicity, per protocol.

Patients must still be followed for adverse events (AEs) for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, or after 30 days (whichever comes first), unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the

investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the CRF.

All patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to grade 1 or 2, or until 30 days after the date of withdrawal (whichever comes first), unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

5 CONCOMITANT THERAPY

Administration of other chemotherapy or immunotherapy, or hormonal therapy, or experimental medications during the study is not allowed. Patients cannot receive radiation therapy while receiving study therapy without previous discussion with the PI.

Supportive care such as granulocyte colony stimulating factor (G-CSF; filgrastim; pegfilgrastim or other biosimilars) may be administered at the discretion of the Investigator. Replacement steroids are permitted. All concomitant treatments, including blood and blood products, must be reported on the source documentation (not necessarily in the CRF). The following concomitant medications **must** be documented on the Con Meds page of the CRF:

- Blood and blood products
- Prophylactic antibiotics
- Premedications (ie, diphenhydramine)
- Antifungals
- Growth factors

No herbal therapies or alternative therapies will be permitted.

Bisphosphonates or denosumab will be allowed for treating osteoporosis or bone metastases.

5.1 DRUG-DRUG INTERACTIONS

5.1.1 LY3023414

Drugs causing QTc interval prolongations should be avoided for all patients in the study.

LY3023414 is a weak inhibitor of cytochrome P450 (CYP)3A4 Drugs that are either sensitive substrates of CYP3A4 or CYP3A4 substrates with a narrow therapeutic range should be administered with caution in combination with LY3023414. In addition, it is recommended to avoid strong inhibitors of CYP3A4 and strong and moderate inducers of CYP3A4 while receiving LY3023414.

Certain fruits, fruit juices and herbal supplements (grapefruit, star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP3A4 isozyme, however, the degree of that inhibition is unknown.[26]

A sample list of drugs that have known interaction with cytochrome P450 can be found here: http://medicine.iupui.edu/flockhart/table.htm.

5.1.2 Prexasertib

On days when prexasertib is administered, patients should avoid taking multiple (more than one) concomitant medications that are known or suspected to cause prolonged QTc or Torsades de Pointes and, if possible, alternative agents should be considered.[27]

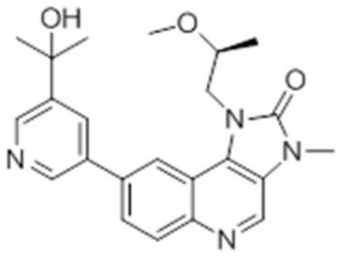
6 THERAPEUTIC AGENTS

6.1 LY3023414

LY3023414 is an investigational, orally available, potent selective inhibitor of the class I PI3K isoforms, mTOR, and DNA-PK. LY3023414 is being evaluated as a monotherapy and in combination with other agents in patients with advanced and/or metastatic solid tumors. Eli Lilly and Company is the manufacturer of LY3023414.[26]

6.1.1 Formulation

LY3023414 is an inhibitor of the PI3K/mTOR pathway; the chemical name is 2H-Imidazo(4,5-c)quinolin-2-one, 8-(5-[1-hydroxy-1-methylethyl]-3-pyridinyl)-1-([2S]-2-methoxypropyl)-3-methyl. LY3023414 is a white to light yellow solid with the molecular formulation $C_{23}H_{26}N_4O_3$ and a molecular weight of 406.48. The chemical structure is below:[26]



LY3023414

6.1.2 Storage and Stability

The drug product is packaged in bottles, which may contain desiccant, and is stable when stored at room temperature conditions according to the label. It is very slightly soluble in water, and slightly soluble in ethanol.[26]

6.1.3 Preparation and Administration

The capsule drug product is composed of LY3023414 with no inactive ingredients, with the exception of the 200-mg capsules, which may also contain colloidal silicon dioxide.

The 10-mg capsules are opaque and orangish-red in color on the body and cap. The 25-mg capsules are opaque and white in color on the body and cap. The 100-mg capsules are opaque and blue in color on the body and cap. The 200-mg capsules are opaque and orangish-red in color on the body and cap.

The tablets are composed of LY3023414 and inactive ingredients such as microcrystalline cellulose, croscarmellose sodium, silicon dioxide, sodium stearyl fumarate, and a colorant.

The 50-mg tablets are green, modified, capsule-shaped tablets. The 100-mg tablets are dark yellow, modified, capsule-shaped tablets. The 150-mg tablets are green, modified, capsule-shaped tablets. The 200-mg tablets are light yellow, modified, capsule-shaped tablets.[26]

6.1.4 Pharmacokinetics

Pharmacokinetic parameters of LY3023414 were evaluated in rats and dogs; data can be found in the prexasertib Investigator's Brochure.[26]

In summary, LY3023414 exposures are generally similar in healthy subjects and cancer patients: in healthy subjects, LY3023414 plasma $AUC_{(0-\infty)}$ and C_{max} are 2760 ng·hr/mL (CV 48%, n=20) and 777 ng/mL (CV 76%, n=20) and in cancer patients LY3023414 blood $AUC_{(0-\infty)}$ and C_{max} are 2710 ng·hr/mL (CV 45%, n=37) and 828 ng/mL (CV 68%, n=54) following LY3023414 200 mg single administration. For further details, please refer to the LY3023414 Investigator's Brochure.[26]

6.1.5 Adverse Effects

For LY3023414 monotherapy (N=108), the most common (that is, occurring in ≥10% of patients) treatment-emergent adverse events (TEAEs) that were considered possibly related to LY3023414 in Study CBBA (N=96) included nausea (36.5%), fatigue (36.5%), vomiting (31.3%), decreased appetite (22.9%), diarrhea (20.8%), rash (13.5%), and oral mucositis (11.5%). Most of these TEAEs were graded as mild or moderate in severity.

LY3023414 monotherapy has been also studied in Asian cancer patients (a Japanese cancer population) in Study CBBH (N=12). The most common (that is, occurring in ≥5 patients) TEAEs that were considered possibly related to LY3023414 in this study included stomatitis (9 patients), nausea (8 patients), decreased appetite (7 patients), and platelet count decreased, anemia, and diarrhea (each 5 patients). Most of these TEAEs were graded as mild or moderate in severity.

The most frequently (that is, occurring in ≥4 patients) reported SAEs regardless of causality within the LY3023414 clinical program included dyspnea (10 patients), nausea and fatigue (each 5 patients), and dehydration, atrial fibrillation, abdominal pain, diarrhea, deep vein thrombosis, and hypotension (each 4 patients).Two deaths were considered due to SAEs (1 case each of pneumonia and pneumonia fungal) which were not related to study treatment. For further details, please refer to the LY3023414 Investigator's Brochure.[26]

Pregnancy

Animal reproduction studies have not been conducted with LY3023414. It is not known whether LY3023414 can affect reproductive capacity in humans. There is no clinical trial experience in pregnant individuals. However, based on data from an embryo–fetal developmental study, LY3023414 has the potential for teratogenicity and embryo/fetotoxicity and, therefore, may result in fetal harm when administered to a pregnant woman. LY3023414 must not be given to pregnant women. To minimize any potential risk, pregnant and breastfeeding women must be excluded from clinical trials of LY3023414. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with LY3023414 and should be administered pregnancy tests prior to each cycle of treatment. Investigators should advise men to avoid

fathering a child during therapy with LY3023414. Both males and females with reproductive potential must agree to use medically approved contraceptive precautions during the study and for at least 3 months following the last dose of the study drug. Upon documentation of pregnancy, the patient must be removed from the study and treatment with study drug(s) must be stopped immediately.[26]

Nursing Mothers

There are no available data on the effects of inhibition of PI3K and mTOR pathway on lactation. The potential effects of LY3023414 use during lactation are not known. Women who are breastfeeding should not take LY3023414.[26]

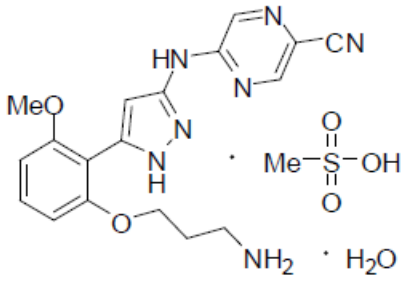
Please see the Investigator's Brochure for additional adverse events and complete drug information.

6.2 PREXASERTIB (LY2606368)

Prexasertib mesylate monohydrate (hereafter, and on the cover page, referred to as prexasertib) is an investigational, adenosine triphosphate–competitive selective inhibitor of checkpoint kinase 1 (CHK1). Prexasertib is being developed as a treatment for patients with advanced cancer and may have utility both as a single agent and in combination with other DNA-damaging agents or targeted agents. Eli Lilly and Company is the manufacturer of prexasertib.[27]

6.2.1 Formulation

Prexasertib is an inhibitor of CHK1; the chemical name is 2-pyrazinecarbonitrile, 5-[[5-[2-(3-aminopropoxy)-6-methoxyphenyl]-1H-pyrazol-3-yl]amino] monomesylate monohydrate. Prexasertib is a yellow to white solid with the molecular formulation $C_{18}H_{19}N_7O_2 \cdot CH_4O_3S \cdot H_2O$ and a molecular weight of 479.51. The chemical structure is below:[27]



6.2.2 Storage and Stability

The drug product, prexasertib for injection, is supplied for clinical trial use as a lyophilized, yellow to white solid in glass vials and is composed of prexasertib mesylate monohydrate and the inactive ingredient sulfobutylether-β-cyclodextrin (Captisol). The drug product is available as either a 40 mg or 20 mg strength vial of the base compound prexasertib. The 40-mg strength vial

contains a 3% excess and the 20 mg strength contains a 5% excess to facilitate the withdrawal of the label amount for application with an appropriate device, such as an infusion set.

The drug product is stable when stored at room temperature. The reconstituted formulation is stable for at least 24 hours at room temperature; however, because the reconstituted drug product does not contain a preservative, the unused solution must be discarded after 12 hours.[27]

6.2.3 Preparation and Administration

Reconstituting the 40-mg or 20 mg vial contents with 19 mL or 10 mL of water, respectively, yields a clear yellow solution with a concentration of 2 mg/mL of prexasertib, pH 4 to 6, and an osmotic pressure ratio of 344 mOsm.

The reconstituted solution may be diluted with dextrose 5% injection before administration. Prexasertib is incompatible with solutions containing saline or lactated Ringer's and must not be mixed or administered simultaneously with other drugs through the same infusion line. A separate document detailing specific instructions regarding filtering and drug administration will be provided by Eli Lilly and Company for the clinical study.

Prexasertib should be handled according to standard procedures and precautions consistent with a cytotoxic anticancer drug.[27]

6.2.4 Pharmacokinetics

The plasma toxicokinetics of prexasertib were evaluated in rats and dogs; data can be found in the prexasertib Investigator's Brochure.[27]

Pharmacokinetic data are available for prexasertib from a total of 146 patients from Parts A, B, and C from Study JTJA, 153 patients across the dose range of 20 to 105 mg/m^2 from Parts A, B, C, D, and E of Study JTJF, 26 patients from JTJI, 9 patients from JTJL, 116 patients from JTJH, 100 patients from Study JTJN, 12 patients in Study JTJK, and 6 patients from Study JTJG. For further details, please refer to the prexasertib Investigator's Brochure.[27]

6.2.5 Adverse Effects

The safety profile of prexasertib is consistent with toxicities commonly observed with standard-of-care cytotoxic agents used to treat cancer (for example, neutropenia, thrombocytopenia, and anemia). Complications from these toxicities such as febrile neutropenia, infections, and clinically significant bleeding events can be mitigated by supportive care approaches such as administration of granulocyte-colony-stimulating factor (G-CSF) and transfusions. Nonhematologic toxicities deemed related to prexasertib treatment occur at a much lower frequency and severity, with fatigue, nausea, diarrhea, decreased appetite, and vomiting being the mostly commonly observed events. Infusion-related reactions have been observed in patients who received prexasertib. For further details, please refer to the prexasertib Investigator's Brochure.[27]

Prexasertib and QTc

In nonclinical toxicology studies in dogs, dose-progressive prolongation of QRS duration and QTc interval was observed. Across Studies JTJA and JTJK, the largest mean QTcF increases from baseline (<15 ms) occurred at the end of the prexasertib infusion. On average, increases in

QTcF values from baseline were <10 ms 1 to 2 hours following the end of infusion and returned to predose values within approximately 24 hours. Taken together, since prexasertib is given IV and concentrations decline quickly after the end of infusion, the observed QTcF changes would be transient in nature and are not considered an important risk to patients at this time.

In Study JTJA, the maximal QTcF increase from baseline was 39 ms and no event of QTcF prolongation was associated with an SAE. Across the program, Torsades de Pointes or serious arrhythmias have not been reported.

Electrocardiograms should be evaluated for changes in QT/QTc interval. Patients with additional risk factors for Torsades de Pointes, including heart failure, a prolonged QTc interval >470 ms on screening ECG, or a family history of long QT syndrome, should be excluded from clinical trials. On days when prexasertib is administered, patients should avoid taking multiple (more than 1) concomitant medications that are known or suspected to cause prolonged QTc or Torsades de Pointes and, if possible, alternative agents should be considered. In addition, at the start of the study and on days when prexasertib is administered, care should be taken to ensure that there are no abnormal levels of electrolytes that could increase the risk for ECG changes.[27]

Pregnancy

The potential treatment effects of prexasertib use during pregnancy and lactation are not known. Nonclinical studies of prexasertib on pregnancy and fetal development have not been performed. To minimize any potential risks, men and women with reproductive potential should use medically approved contraceptive precautions during treatment and for 3 months after the last dose of prexasertib.[27]

Nursing Mothers

The potential treatment effects of prexasertib use during lactation are not known. Women who are breastfeeding should not receive prexasertib.[27]

Please see the Investigator's Brochure for additional adverse events and complete drug information.

7 INVESTIGATIONAL PLAN

7.1 REGISTRATION PROCEDURES

Written documentation of full, noncontingent IRB approval must be on file before a patient can be registered. The registration process begins when the Coordinator has obtained a signed informed consent.

A patient identification number is directly assigned once the patient is found eligible. Patient ID, consent date, status of patient (eg, active or screen failure), relevant comments, and date of patient discontinuation are to be recorded on the Patient Log by the Coordinator. The Patient Log will be kept in a binder for review for any reason (ie, monitoring/audit). Once a patient ID is assigned, this will constitute the registration confirmation. **Treatment must begin within 20 working days (not counting the day of dosing) after the patient's registration on the study.**

The PI may be allowed the opportunity to review and grant exceptions for minor deviations in eligibility, in order to maximize patient accrual without jeopardizing patient safety or scientific integrity of these studies. Examples might include minor deviations of baseline labs, timing of prior treatment or tests, etc. It is recognized that these questions arise frequently. The procedure to be followed is for the Investigator or his/her representative (eg, research nurse) to e-mail the request to the PI for an exception. The PI would then make a determination, which is binding. In no instance should this exception constitute a safety issue for the patient or a significant deviation from the scientific purpose of the study.

7.2 STUDY TREATMENT ADMINISTRATION

Patients will receive prexasertib as an approximately 60-minute infusion on Day 1 and Day 15 of a 28-day cycle. Oral LY3023414 will be administered twice a day (BID) on Days 1 to 28 of a 28-day cycle. On prexasertib dosing days, the administration of LY3023414 will follow immediately after the end of the prexasertib infusion (within 5 minutes) on Day 1 of each cycle. Patients should take the morning and evening doses of LY3023414 approximately 12 hours apart (preferably within a 10- to 14-hour range). Please refer to Sections 7.2.2.1 and 7.2.2.2 for further details.

7.2.1 Premedications

LY3023414

There is no required premedication for the administration of LY3023414.[26]

Prexasertib

Premedication with diphenhydramine hydrochloride 25-50 mg IV and/or other equivalent premedication may be administered at the physician's discretion.[27]

7.2.2 Treatment Plan

1. Once patients sign informed consent, they will be evaluated with a complete history, physical examination as well as initial studies as described in Section 8.1.
2. Metastatic TNBC patients will undergo core needle biopsies of a metastatic lesion for NGS, RPPA, and other molecular analyses at study entry.
3. Patients will then be treated with 150 mg LY3023414 PO BID and prexasertib 80 mg/m^2 IV administered every 2 weeks until disease progression or unacceptable toxicity.
4. Any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion, a second core needle biopsy of the same metastatic lesion (or different metastases if the initial metastasis has regressed) disease will be performed for RPPA and other molecular analyses. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.
5. Treatment will be discontinued in patients who achieve a confirmed clinical complete response, and these patients will be followed to document the durability of the complete responses.
6. Patients whose disease does not respond to the combination of LY302314 and prexasertib may be treated with standard of care breast cancer therapies **off study**, at the

recommendation of the treating physician.

The treatment schema is shown in Table 1.

Table 1. Treatment schema

Agent	Dose	Frequency of administration	Route of administration
LY3023414[a]	150 mg	BID	PO
Prexasertib	80 mg/m^2	Days 1 and 15 of 28 days	IV

[a] Doses are administered orally BID approximately 12 hours apart on Days 1 through 28 of each 28-day cycle.

7.2.2.1 LY3023414

Doses are administered orally BID approximately 12 hours apart (preferably within a 10- to 14-hour range) on Days 1 through 28 of each 28-day cycle. LY3023414 capsules should be taken at approximately the same time on each dosing day. LY3023414 may be administered with or without food. Patients may experience improved GI tolerability of LY3023414 when it is taken with or just after a meal. Patients should also be monitored in order to detect and treat mucositis/stomatitis early before it becomes severe.

On prexasertib dosing days, patients will receive prexasertib first (see Section 7.2.2.2). The administration of LY3023414 will follow immediately at the end of the prexasertib infusion (within 5 minutes of infusion end).

If the patient misses a dose of LY3023414, the patient should take the dose as soon as possible, but not less than 6 hours before the next dose is due for BID dosing. If the next dose is due in less than 6 hours, the patient should skip the missed dose and take the next dose as scheduled.

LY3023414 should be stored within the temperature range stated on the label. Patients should be instructed to store the drug product at home in the provided container and to keep out of the reach of children. The drug product should not be crushed or dissolved. Capsules should not be opened.[26]

7.2.2.2 Prexasertib

Prexasertib is administered as an IV infusion over 1 hour using a central or free-flowing peripheral IV line with an appropriate filter. Prexasertib should not come in contact with normal saline; the infusion line should be flushed with dextrose 5% injection before and after prexasertib administration.

On prexasertib dosing days, patients will receive prexasertib first. The administration of LY3023414 will follow immediately at the end of the prexasertib infusion (within 5 minutes of infusion end).

There is a low incidence of infusion reactions: In the event of a suspected infusion-related reaction, institutional guidelines for managing infusion reactions should be followed. For subsequent infusions, premedication with diphenhydramine and/or other premedication (see

Section 7.2.1) may be administered at the physician's discretion. The infusion rate may also be decreased by up to 50% after recovery from the infusion-related reaction. The patient should be monitored for signs and symptoms indicative of an infusion-related reaction.

The actual doses of prexasertib to be administered are determined by calculating the BSA for each patient at the beginning of each cycle.[27]

7.2.3 Treatment Delay

Patients will be allowed to stay on either of the therapies if they need to delay one for toxicity. If a treatment day variation is needed for reasons other than toxicity, an attempt should be made to keep the variation within the following parameters: **±4 calendar days for 28-day cycles.** Any delay within this window is NOT a deviation. **Note**: This delay window **does not** apply to Cycle 1.

1. Treatment (either one or both therapies) may be delayed no more than 3 weeks for any reason.
2. Patients who are off study treatment for more than 3 weeks for any reason will be considered off treatment.
3. If patients miss doses for less than 2 weeks due to toxicities, the doses will not be made up.
4. If patients miss doses for less than 2 weeks due to reasons other than toxicity (car broke down, missed the bus, etc), the doses will be made up.

7.2.4 Dose Modification for Toxicity

Dose reductions are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 as linked in Appendix I. At each clinic visit, treatment with LY3023414 or with prexasertib will continue if:

- ANC ≥1000 (if pegfilgrastim is being used) or of ≥1200/mm^3 (if no pegfilgrastim is being used)
- Platelets ≥75,000/mm^3
- Resolution of nonhematologic toxicities to ≤Grade 1 or baseline

7.2.4.1 LY3023414 Dose Modifications

Dose reductions will be at the physician's discretion. Two dose reductions are permitted for LY3023414. Dose reductions beyond Level -2 would result in discontinuation of treatment. Re-escalation to the previous dose is acceptable in the absence of continuing toxicity, provided that this dose is not greater than current dose being tested. If subsequent dose reduction is required after re-escalation, the patient must be maintained at the reduced dose level for all remaining cycles.

The dose reduction levels for LY3023414 are shown in Table 2.

Table 2. LY3023414 Dose Reduction Levels	
Level	**LY3023414**
Starting Dose (Level 0)	150 mg Q12H
Level -1	100 mg Q12H
Level -2	100 mg Q24H
Abbreviations: Q12H = every 12 hours; Q24H = every 24 hours	

Nonhematologic Toxicity:

For nonhematologic toxicities that are ≤ grade 2, manage symptomatically if possible, and resume without dose reduction.

For nonhematologic Grade 3 or 4 toxicities (excluding nausea and alopecia), the treatment should be withheld until the patient recovers completely or to Grade 1 toxicity. This reduction should be permanent. If the treatment was withheld for more than 3 weeks, the patient will be taken off treatment.

Hematologic Toxicity:

Treatment decisions and dose reductions should be made based on ANC and platelet counts on the day of treatment administration. A reduction due to low hematologic values on the day of treatment is not permanent and is made on each treatment visit. Dose modifications must be recorded on the CRF.

- Patients must have ANC of $\geq 1000/mm^3$ on Day 1 of each cycle (if pegfilgrastim is being used) or of $\geq 1200/mm^3$ on Day 1 (if no pegfilgrastim is being used) to receive scheduled treatment. Treatment may be delayed to allow sufficient time for recovery.
- Patients must have a platelet count of $\geq 75{,}000/mm^3$ on Day 1 of each cycle to receive scheduled treatment. LY3023414 should be delayed until platelet counts recover to $\geq 75{,}000/mm^3$ and then treated with either full dose or reduced dose at the physician's discretion. Treatment may be delayed to allow sufficient time for recovery.

Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and guidance from Eli Lilly.

7.2.4.2 Prexasertib Dose Modifications

Dose modifications will be at the physician's discretion. One dose reduction and one dose escalation are permitted for prexasertib. Dose reductions beyond Level -1 would result in discontinuation of treatment.

Patients who tolerate Cycles 1 and 2 without Grade 4 hematologic or Grade 3-4 nonhematologic toxicity may have the prexasertib dose increased on Cycle 3 to Level +1 ($105 mg/m^2$) at the physician's discretion.

The dose modification levels for prexasertib are shown in Table 3.

Table 3. Prexasertib Dose Modification Levels	
Level	**Prexasertib**
Level +1[a]	105 mg/m^2
Starting Level 0	**80 mg/m^2**
Level -1	60 mg/m^2
Abbreviations: Q12H = every 12 hours; Q24H = every 24 hours [a]Patients who tolerate Cycles 1 and 2 without Grade 4 hematologic or Grade 3-4 nonhematologic toxicity may have the prexasertib dose increased on Cycle 3 to Level +1 at the physician's discretion.	

Additional dose adjustments and delays are below in Table 4:

Table 4. Additional dose adjustment guidance for prexasertib			
Toxicity	**CTCAE Grade**	**Action**	**Dose Adjustments and Considerations**
Neutropenia	Grade 3 or 4	Delay treatment until ≤Grade 2 (≥1000/mm^3 if pegfilgrastim is being used, or ≥1200/mm^3 if no pegfilgrastim is used)	Investigator discretion; consider prophylactic G-CSF
Thrombocytopenia	Grade 3 or 4	Delay treatment until ≤Grade 1 (≥75/mm^3)	Investigator discretion
Anemia	Grade 3 or 4	Consider RBC transfusion or EPO (if consistent with institutional guidelines). Treatment may proceed or be delayed at the discretion of the investigator.	Investigator discretion
Febrile neutropenia (without prophylactic G-CSF)	Any grade	Delay treatment until afebrile and neutrophils ≤Grade 2 (≥1200/mm^3)	Investigator discretion; consider prophylactic G-CSF
Febrile neutropenia (with prophylactic G-CSF)	Any grade	Delay treatment until afebrile and neutrophils ≤Grade 2 (≥1000/mm^3)	Reduce to next lower dose level unless there is documented agreement between investigator and CRP/CRS
Allergic/hypersensitivity reaction[a]	Grade 1 or 2	Administer treatment per institutional guidelines for allergic/hypersensitivity reactions. Monitor closely for any worsening symptoms. A reduced rate can be used for subsequent infusions.	Investigator discretion
	≥Grade 3	Stop infusion immediately and disconnect infusion tubing from the patient. Administer treatment per institutional guidelines. Patient must not receive any further treatment with prexasertib.	

Other nonhematologic toxicity[b]	Grade 2	Delay treatment until ≤Grade 1 or baseline[c]	Investigator discretion
	Grade 3 or 4	Delay treatment until ≤Grade 1 or baseline[c]	Reduce to next lower dose level

Abbreviations: CRP = clinical research physician; CRS = clinical research scientist; CTCAE = common terminology criteria for adverse events version 4.0; EPO = erythropoietin; G-CSF = granulocyte colony stimulating factor; RBC = red blood cells.
[a] Please refer to the IB for the most recent guidance on allergic/hypersensitivity reactions.
[b] Except alopecia, fatigue, or toxicities that can be controlled with adequate treatment such as nausea, vomiting, diarrhea, or asymptomatic electrolyte disturbances.
[c] Baseline is considered prior to dosing on Cycle 1 Day 1.

Nonhematologic Toxicity:

For nonhematologic toxicities that are ≤ Grade 2, manage symptomatically if possible, and resume without dose reduction.

For nonhematologic Grade 3 or 4 toxicities (excluding nausea and alopecia), the treatment should be withheld until the patient recovers completely or to Grade 1 toxicity. This reduction should be permanent. If the treatment was withheld for more than 3 weeks, the patient will be taken off treatment.

Hematologic Toxicity:

Treatment decisions and dose modifications should be made based on ANC and platelet counts on the day of treatment administration (see Table 4 for guidance). A reduction due to low hematologic values on the day of treatment is not permanent and is made on each treatment visit. Dose modifications must be recorded on the CRF.

- Patients must have ANC of ≥1000/mm^3 on Day 1 of each cycle (if pegfilgrastim is being used) or of ≥1200/mm^3 on Day 1 (if no pegfilgrastim is being used) to receive scheduled treatment. Treatment may be delayed to allow sufficient time for recovery.
- Patients must have a platelet count of ≥75,000/mm^3 on Day 1 of each cycle to receive scheduled treatment. Prexasertib should be delayed until platelet counts recover to ≥75,000/mm^3 and then treated with either full dose or reduced dose at the physician's discretion. Treatment may be delayed to allow sufficient time for recovery.

Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and guidance from Eli Lilly.

7.3 TOXICITY

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as linked in Appendix I. This document can also be downloaded from the Cancer Therapy Evaluation Program (CTEP) home page <http://ctep.cancer.gov>. Events must be documented on the AE page of the CRF.

8 SCHEDULE OF ASSESSMENTS

The schedule of assessments for the trial is shown in Appendix II. If a required observation or procedure is missed, documentation is required in the source records, on the Protocol Deviation Form, and on the CRF, to explain the reason for this protocol deviation.

For scheduling purposes, Day 1 is the first day of treatment administration. Return appointments must always be scheduled from Day 1 of the study. It is imperative that all visits occur within the specified windows.

8.1 PRESTUDY ASSESSMENTS

Note: Assessments that are part of the standard of care and obtained within 3-4 weeks of the prestudy assessment visit are acceptable as part of the screening tests. Results of such tests will be acceptable even if obtained prior to the execution of the Inform Consent Form.

Prior to entry into the study, the following assessments will be performed to determine if patient is eligible to continue in the study as per Sections 4.2 and 4.3 describing the inclusion and exclusion criteria for the study.

1. A signed Patient Informed Consent Form must be obtained.
2. A signed Patient Authorization Form (HIPAA) must be obtained.
3. It has been confirmed that the patient meets **all** inclusion criteria and **none** of the exclusion criteria.
4. A complete medical history must be obtained **within 4 weeks prior to registration**.
5. A complete physical examination (including vital signs, height, and body weight) must be obtained **within 4 weeks prior to registration**.
6. Assessment of PS on the ECOG scale (Appendix III) must be obtained **within 4 weeks prior to registration.**
7. Assessment of concomitant medications must be obtained **within 4 weeks prior to registration.**
8. A complete blood count (CBC) with differential and platelet count **within 4 weeks prior to registration.**
9. Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium), must be performed **within 4 weeks prior to registration**.
10. Assessment of magnesium (Mg) and phosphorus (P) **within 4 weeks prior to registration**.
11. HbA1c must be performed **within 4 weeks prior to registration.**
12. Fasting serum glucose must be performed **within 4 weeks prior to registration.**
13. Females of childbearing potential must have a serum pregnancy test performed **within 7 calendar days prior to registration**. Women of child-bearing potential participating must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception during treatment with study drug and for at least 12 weeks following the last dose of study drug.
14. ECG must be performed **within 4 weeks prior to registration**.
15. A clinical assessment of the patient's disease (ie, by physical examination) must be performed **within 4 weeks prior to registration**.

16. Radiological assessment of tumors (ie, chest and abdomen CT scan) must be performed **within 8 weeks prior to registration**. The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time.
17. Assessments of other lesions by physical exam must be performed **within 4 weeks prior to registration**.
18. If safely accessible, research biopsies of the patient's metastatic locoregional or pulmonary or hepatic disease must be obtained **prior to the first day of treatment**. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted. If a skin biopsy cannot be safely obtained, patients may still be eligible, per physician discretion.
19. Whole blood collection (40 mL) for germline exome sequencing studies.
20. Distribution of LY3023414 dosing and treatment adverse events patient diaries (see Appendix V).

8.2 ASSESSMENTS DURING TREATMENT

The following assessments will be performed during therapy on Day 1 prior to the start of each cycle, unless otherwise specified. **A Cycle is defined as 28 days (prexasertib dosing on Day 1 and 15)**.

There is a window (**up to 4 calendar days prior to the scheduled time point**) for assessments during the study. Any delay within this window is NOT a deviation. Assessments that are to be done on days when study drug is administered must be done **prior to dosing** as these assessments (CBC, CMP, assessment of response, etc) may determine whether or not drug is administered, or if a dose reduction is necessary, unless otherwise noted.

Note for Cycle 1 only: the prestudy assessments that correspond to assessments below may be used as Cycle 1 assessments as long as they are completed within the 72 hours prior to the patient receiving their first dose of study drug. If more than 72 hours have elapsed since the prestudy assessment, the assessment must be repeated for Cycle 1.

1. A brief medical history, to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history should be recorded on the AE page of the CRF.
2. A brief physical examination, including vital signs and body weight
3. ECOG PS (Appendix III)
4. Assessment of concomitant medications
5. A CBC with differential and platelet count on Day 1 and Day 15 of every cycle
6. A CMP Day 1 and Day 15 of each cycle
7. Assessment of magnesium (Mg) and phosphorus (P) Day 1 and Day 15 of each cycle
8. HbA1c must be obtained Day 1 and Day 15 of each cycle
9. Fasting serum glucose must be obtained Day 1 and Day 15 of each cycle
10. A pre-dose ECG (within 10 minutes of beginning prexasertib infusion) must be obtained on Cycle 1 and Cycle 2. Additional ECG may be obtained if clinically indicated.
11. A post-dose ECG (within 10 minutes of ending prexasertib infusion) must be obtained on Cycle 1 and Cycle 2. Additional ECG may be obtained if clinically indicated. **NOTE:** it is

preferred to complete the post-dose ECG upon completion of the prexasertib infusion, but prior to LY3023414 dosing.

12. Tumor response by clinical assessment of the patient's disease (ie, by physical examination)
13. Radiological assessment of tumors (ie, chest and abdomen CT scan) every 8 weeks or as clinically indicated. The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time.
14. Assessments of other sites of disease must be performed **only to confirm a CR**.
15. Toxicity
16. If safely accessible, research biopsies of the same metastatic lesion (or different metastases if the initial metastasis has regressed) may be obtained **any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion**. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.
17. Whole blood collection (40 mL) for germline exome sequencing studies **any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion**.
18. Patient diary assessment of LY3023414 dosing and treatment adverse events

8.3 OFF TREATMENT/END OF TREATMENT ASSESSMENTS

This is a single assessment that will be performed within 30 days ± 2 days when a patient finishes treatment or goes off treatment because of PD, toxicity that places patients off treatment, if patients achieve a confirmed clinical complete response, or in cases of physician decision or where patient withdraws consent. Patients who withdraw consent may not want any further assessments; however, they should be encouraged to have these final assessments done.

NOTE: End of treatment, or off treatment, is NOT considered off study or withdrawn from the study.

The following evaluations will be performed at this visit:

1. A brief medical history should be done to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history should be recorded on the AE page of the CRF.
2. A brief physical examination, including vital signs and body weight.
3. A CBC with differential and platelet count.
4. A CMP
5. A serum pregnancy test
6. A tumor clinical assessment of the patient's disease (ie, by physical examination)
7. A toxicity assessment
8. Collection of any outstanding patient diaries

8.4 FOLLOW UP ASSESSMENTS

The duration of patient participation in the study will be a maximum of 18 months, which is counted **from the start of treatment**, provided progressive disease has not occurred. Follow-up visits will be performed **every 3 months for 1 year from the date of last treatment dose**. Only research data will be collected during this time.

Note: Patients who die or withdraw consent are considered **off study** and no further information will be collected.

1. Additional therapy
2. Date and site of relapse or progression
3. Survival status
4. Toxicities will be recorded for the first 30 days following the last study treatment.
5. Clinical and radiological tumor assessment as per standard of care

8.5 BLOOD SAMPLES FOR EXOME SEQUENCING

Whole blood collection (40 mL) for exome sequencing studies will be obtained at baseline and any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion

No information that identifies the patient will be given to any of the laboratories that will analyze blood samples. Any material analyzed will be supplied with code number identifiers only, without the patient's name or other identifying information. Access to the database which contains patient identifiers is limited to study investigators and project managers only and is safeguarded by a password protection system. Passwords are not shared. If research findings are published from this study, the research patient will not be identified by name.

8.6 BIOPSIES

Research biopsies will be obtained at the following time points (See Appendix IV for tissue collection and handling):

- A minimum of four 14-gauge needle biopsy cores (or the largest core biopsy deemed safe) may be collected at baseline, prior to the initiation of treatment.
- A minimum of four 14-gauge needle biopsy cores (or the largest core biopsy deemed safe) may be collected any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion.

Second research biopsies may be obtained from a different metastasis if the initial metastasis has regressed. Tissue biopsies of a patient's metastatic locoregional or pulmonary or hepatic disease will be analyzed by next generation sequencing (NGS) for mutations in DNA repair and PI3K pathways, as well as others. Remaining tissue will be frozen and/or formalin-fixed paraffin embedded (FFPE) for biomarker development.

If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.

9 SAFETY EVALUATIONS

9.1 ADVERSE EVENTS

All Grade 3 and 4 adverse events (AEs), Grades 1 and 2 alopecia, and all grades of neutropenia will be recorded in the CRF throughout the trial. In addition, all treatment-related Grade 1 and 2 laboratory abnormalities, which are deemed "clinically significant" by the Treating Physician will be documented in the CRF.

Adverse events (AEs) will be recorded throughout the trial. Toxicities and AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as linked in Appendix I. The events, and the relationship of each event to treatment, will be assessed by the Treating Physician and recorded on the CRF. Additional information about each event, such as treatment required, eventual outcome, and whether or not therapy had to be interrupted or dosages reduced, will also be recorded on the CRF. Adverse events will be recorded for up to 30 days following the last study treatment.

Definitions and additional reporting instructions are provided in Part II of this protocol.

9.2 LABORATORY DATA

For the treatment of the patient, laboratory data will be obtained according to the schedule of assessments. Only the laboratory data requested on the CRF need to be recorded on the appropriate laboratory CRF page. In addition, abnormal results that are associated with an AE will be documented on the Adverse Event page of the CRF if the laboratory abnormality fits the definition of an AE or can potentially result in an AE.

10 EFFICACY ASSESSMENTS (SOLID TUMOR)

All efficacy assessments will be investigator assessments of response, time to response, and duration of response. Investigator will determine objective response rate, complete response (CR), partial response (PR), stable disease (SD), or progression of disease (PD).

11 STATISTICAL CONSIDERATIONS

11.1 POPULATIONS FOR ANALYSIS

11.1.1 Analysis Populations

Intent-To-Treat (ITT) Population: Includes all patients registered on the study (eligible and ineligible). This population will be included in overall patient listings, in summary tables of patient demographics and baseline disease characteristics, and also in the list of treatment discontinuations after enrollment.

Evaluable Population: Includes all eligible patients who meet the protocol-specified efficacy analyses requirements and who have received at least 1 dose of study drugs. This population will comprise those patients who will be assessed for pathologic response. Early discontinuation of treatment (in Cycles 1-2), secondary to toxicity, will be considered a treatment failure. If death occurs before the completion of 1 cycle, the patient will be reported as evaluable, early death, but deemed not evaluable for response.

Safety Population: Includes all patients (eligible and ineligible) who receive at least 1 dose of study drugs. This safety population will also be used for the summaries and analysis of all safety parameters (drug exposure, tables of adverse events information, including serious adverse events, etc.). Adverse events that are unrelated to treatment and that occur >30 days after the administration of treatment will not be reported or analyzed.

11.1.2 Patient Characteristics

Patient characteristics including demographics and pretreatment characteristics, breast mass and axillary lymph node size, staging evaluation at baseline, medical history, and family history will be summarized. Descriptive statistics including sample size, mean, standard deviation, median, and minimum and maximum values will be presented for continuous variables. Frequency distributions will be presented for categorical variables.

11.1.3 Patient Disposition

Patient disposition including the number of patients enrolled, completed, and discontinued from the study will be summarized overall and by study site. The reasons for discontinuation will also be summarized, and patients who discontinued will be listed.

11.2 HYPOTHESIS AND ENDPOINTS

The hypothesis of this proof of concept pilot trial is that administration of LY3023414 and prexasertib will inhibit NHEJ in metastatic TNBC.

This is an exploratory and descriptive clinical trial in which the primary objective is to assess the objective response rate associated with LY3023414 and prexasertib in metastatic triple negative breast cancer patients.

The secondary objectives of this trial are to assess the duration of response; assess the metastatic TNBC tissues for homologous recombination proficiency and deficiency; and assess expression of phosphorylated proteins involved in homologous recombination.

11.3 SAMPLE SIZE

Ten patients will be enrolled over 12-18 months.

11.4 STATISTICAL METHODS

Ten patients with metTNBC will be enrolled on study and will be treated with LY3023414 and prexasertib. If 0-1 of 10 patients has an objective response to treatment, enrollment will be stopped. If at least 2 of 10 patients has an objective response with treatment, an additional 10 patients could be enrolled on study, following discussion and agreement with Lilly. Expanding the number of patients to 20 would require a protocol amendment. With a sample size of 20 patients, there is an 60% chance of observing 4 or more responses if the true response rate is at least 20%. The complete response rate and duration of response will also be assessed to determine if the combination of LY3023414 and prexasertib will produce exceptional responses of at least 12 months in duration.

A 30% or greater rate of durable (at least 12 months) complete or partial responses would be of high clinical interest and would justify further development of this therapeutic strategy.

PART II – PROCEDURES

12 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All AEs, regardless of severity, will be followed up by the Investigator until resolution is satisfactory. All AEs will be recorded for up to 30 days following the last study treatment.

12.1 DEFINITIONS

12.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

12.1.2 Serious Adverse Event

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,

  (NOTE: Any death from any cause while a patient is receiving treatment on this protocol, or ≤ 30 days following the last dose of protocol treatment must be reported.)

- Is life-threatening,

  (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization,

  (NOTE**:** Hospitalization is considered an overnight stay, therefore visits to hospital, without admission, are not considered serious unless they meet another criterion, (eg, medically significant). Planned surgery, or planned admission for study drug, is not considered an SAE unless, the hospitalization is prolonged or if another criterion is met.)

- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Additionally, important medical events that may not be immediately life threatening or result in death or hospitalization, but that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

  Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.1.3 Unexpected Adverse Event

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational medicinal product).

12.2 REPORTING

12.2.1 Adverse Events

Adverse events will be recorded for the duration of a patient's study treatment, and for up to 30 days following the last study treatment. All AEs, regardless of causal relationship are to be recorded in the source documentation. Only those specified in Section 9.1 are to be recorded in the CRF. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis should be documented as the AE/SAE and not the individual signs /symptoms.

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as linked in Appendix I. The event, and the relationship of each event to treatment, will be assessed by the Investigator and recorded on the CRF. Additional information about each event, such as treatment required, whether or not therapy had to be interrupted or dosages reduced, and eventual outcome will also be recorded on the CRF.

Pre-existing conditions will be recorded at baseline on the Medical History Form. If a pre-existing condition does not change, it does not have to be reported as an AE on **subsequent** cycles.

12.2.2 Serious Adverse Event

All SAEs will be reported per Baylor standard operating procedure (SOP) within 24 hours of becoming aware of the event. All SAEs will be reported by completing a SAE Report Form and emailing the form to the PI. Baylor IRB will be notified via iRIS.

SAEs will be reported to Lilly as soon as possible and no later than 1 business day of the Investigator and/or Institution receiving notification of any serious adverse event experienced by a patient participating in the study and receiving study drug. The preferred method of SAE reporting is via the Lilly Investigator Initiated Research (IIR) portal:

https://www.lillyinvestigatorresearch.com

However, fax is also acceptable to report SAEs to the local safety representative using the following:

Local fax number: 866-644-1697

Local telephone number: 800-545-5979

All SAEs must be documented on the Serious Adverse Event Report Form and on the adverse event CRF page. The event term used on the SAE report should match the term in the CRF.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the as soon as it is available. For unexpected fatal, life-threatening, or other unexpected SAEs, follow-up information must be reported per Baylor SOP.

12.2.3 Discontinuation of Patient

Discontinuation of a patient on study for the occurrence of a serious or unexpected AE associated with the use of the study medication should be reported to the PI and Project Manager.

12.3 PREGNANCY

Patients of child-bearing potential participating must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception during treatment with study drug and for at least 12 weeks following the last dose of study drug.

Note: Unless not allowed by local regulations, patients of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative pregnancy test at the screening visit (prior to biopsy) and within 24 hours prior of drug exposure.

If pregnancy is confirmed in a patient during the course of the study, the patient must be taken off treatment and the pregnancy must immediately be recorded on the source documents and CRF, and will be reported by completing the Pregnancy Notification Form and emailing the form to the PI. Any pregnancy that occurs in a female partner of a male study participant will also be immediately recorded on the source documents and CRF and will be reported by completing the Pregnancy Notification Form and emailing the form to the PI. In addition, the Investigator must report to the Baylor IRB any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 8 weeks.

13 PROTOCOL AND DATA DEVELOPMENT

13.1 ETHICS

13.1.1 Institutional Review Board

This protocol will be implemented only after review and full approval of the protocol and the Patient Informed Consent Form has been obtained from a properly constituted IRB. This written approval must be dated and it must clearly identify the protocol, any amendments, the Patient Informed Consent Form, and any applicable recruiting materials and subject compensation programs approved.

During implementation of this protocol, the PI is required to send various documents to the IRB for review:

1. Changes to the current protocol.
2. All protocol amendments and Patient Informed Consent Form revisions.

3. Required progress reports.

Particular attention is drawn to the Food and Drug Administration (FDA) regulations regarding the IRB. The PI is responsible for the initial and continuing review and approval of the proposed clinical study in accordance with these regulations. At least once a year, the IRB will be asked to review and re-approve the tissue collection protocol; the request must be documented in writing. At the end of the trial, the PI will notify the IRB that the trial has been completed.

13.1.2 Patient Informed Consent

The informed consent should meet the requirements of the latest version of the Declaration of Helsinki and any applicable regulations and guidelines. It must be approved by an institutional ethics committee/IRB.

Prior to entry into the trial and before any protocol-required procedures are performed, the Investigator must explain the nature of the trial, its intended purpose, and the implications of participation to potential patients or to their legal representatives. They will be told about the possible risks and benefits, and the possible adverse experiences. They will be informed that patients' participation is voluntary, and that they may withdraw consent to participate at any time. They will also be informed that if patients choose not to participate in the trial, alternative treatments are available; such refusal will not prejudice further treatment of their disease. Potential patients or their legal representatives must be given the opportunity to ask questions about the trial protocol and the procedures involved.

Finally, each patient will be told that his or her records may be accessed by authorized personnel and other authorized individuals without violating the patient's confidentiality, to the extent permitted by the applicable laws and/or regulations. By signing the written Patient Informed Consent Form, the patient or his or her legal representative is authorizing such access. Following this explanation and prior to entry into the trial, the written, dated, and signed Patient Informed Consent Form must be obtained from each patient or his or her legal representative; a copy will be given to the person signing the form.

13.1.3 Confidentiality of Records

The Investigator is required to retain, in a confidential manner, sufficient information on each patient (eg, full name, current address, and social security number) so that the patient may be contacted by the FDA, should the need arise.

13.2 STUDY RECORDS

13.2.1 Documentation

A log of all patients evaluated for this protocol must be maintained. Patients excluded from admission will be provided with a clear explanation of the specific reasons why they have been excluded from the study. Patients who are included will be assigned a patient identification number.

For each patient treated with the study drug(s), the Research Coordinator is required to prepare and maintain case histories that include all observations and other data pertinent to the

investigation. This will include all source documents needed to verify the accuracy of all observations and other data contained in the CRFs on each study patient.

The Investigator or his/her designee is required to retain the records related to the trial for a period of 2 years following the date a marketing application is approved for the indication being investigated. If no application is to be filed or if the application is not approved for such indication, the records must be retained until 2 years after the investigation is discontinued and the regulatory agencies are notified.

13.2.2 Case Report Form Procedures

Data will be entered at the site using the protocol CRF. The Investigator or his/her designee is responsible for recording all data relating to the trial on the CRFs. The Investigator must verify that all data entries on the CRFs are accurate and correct. CRFs must be completed **within 15 calendar days** of the end of each cycle and **within 15 calendar days** following completion of study therapy.

13.3 MODIFICATION OF PROTOCOL

Any changes to this protocol that affect study objectives, study design, study procedures, patient population, or significant administrative procedures will require a formal amendment to the protocol. Any proposed protocol amendments must be sent in writing to the applicable IRB. Prior to implementation, an amendment must be agreed upon by the PI and approved by the IRB.

General administrative changes to the protocol are minor corrections and/or clarifications that do not affect the manner in which the study is to be conducted. Such administrative changes will be agreed upon by the PI and will be documented in a memorandum. The applicable IRB will be notified of administrative changes according to applicable IRB guidelines.

14 REFERENCES

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Appendix I NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Publish Date: May 28, 2009

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)
Version 4.0

As of May 28, 2009 (v4.03: June 14, 2010), NCI has edited version 4.0 of the Common Terminology Criteria for Adverse Events. These may be obtained at the following web link http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix II Schedule of Assessments

Assessment	**Prestudy** As per 8.1	**During Treatment** ***on Day 1 prior to each cycle, unless otherwise specified*** As per 8.2	**End of Treatment** *up to 30±2 days following* As per 8.3	**Follow-up** ***every 3 months for 1 year from the date of last treatment; research data only*** As per 8.4
Informed consent	✔			
Signed patient authorization (HIPAA)	✔			
Inclusion/exclusion criteria	✔			
Complete medical history	Within 4 weeks prior to registration (PTR)			
Complete physical examination (including vital signs, height, and body weight)	Within 4 weeks PTR			
Brief medical history		✔	✔	
Brief physical exam (vitals, weight)		✔	✔	
Assessment of ECOG PS	Within 4 weeks PTR	✔		
Assessment of conmeds	Within 4 weeks PTR	✔		
CBC with differential and platelet count	Within 4 weeks PTR	✔ [1]	✔	
Complete metabolic profile (CMP)	Within 4 weeks PTR	✔ [1]	✔	
Mg and P	Within 4 weeks PTR	✔ [1]		
HbA1c	Within 4 weeks PTR	✔ [1]		
Fasting serum glucose	Within 4 weeks PTR	✔ [1]		
Serum pregnancy test	Within 7 days PTR		✔	
ECG	Within 4 weeks PTR	✔ [2]		
Clinical assessment of disease	Within 4 weeks PTR	✔	✔	✔
Radiological assessment of disease	Within 8 weeks PTR	As clinically indicated		As clinically indicated
Assessment of other lesions	Within 4 weeks PTR	To confirm CR		
Toxicity/AE		✔	✔	For 30 days following last dose
Research biopsies	Prior to the first day of treatment	After Cycle 2 or physician's discretion[3]		
Whole blood (40 mL)	✔	After Cycle 2 or physician's discretion[3]		
Patient diaries	✔	✔	✔	
Survival, relapse or PD, additional therapy				✔

[1] Day 1 and Day 15 of each 28-day cycle
[2] A pre-dose ECG (within 10 minutes of beginning prexasertib infusion) must be obtained on Cycle 1 and Cycle 2. A post-dose ECG (within 10 minutes of ending prexasertib infusion) must be obtained on Cycle 1 and Cycle 2. Additional ECG may be obtained if clinically indicated. **NOTE:** it is preferred to complete the post-dose ECG upon completion of the prexasertib infusion, but prior to LY3023414 dosing.
[3] Any time after the completion of Cycle 2 of the treatment combination, or at the physician's discretion.

Appendix III ECOG Performance Status Scale

Grade	Description
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 light or sedentary nature—(eg, light housework or office work)
2	Ambulatory and capable of all self care, but unable to carry out any work activities; up and about > 50% of waking hours
3	Capable only of limited self-care, confined to bed or chair >50% of waking hours
4	Completely disabled; cannot carry out any self care; totally confined to bed chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982; 5:649-655.

Appendix IV Research Biopsies and Blood Collection

Tissue Collection Guidelines for Snap Freezing Tissue for Storage

Tissue will be snap frozen according to the Biospecimen and Project Management Core (BPM) protocol. Briefly, immediately after biopsy, tissue will be placed in a screw-capped cryovial, and submerged in liquid nitrogen for rapid freezing and preservation of tissue. Tissue must be transported to the Core in the Baylor Charles A. Sammons Cancer Center on the 6th floor on dry ice. Tissue will then be stored in -80°C freezer until further use.

Blood Collection Guidelines

I. Collections at Clinical Site

a. Blood: Collect 4 tubes of whole blood in 10 mL purple-top EDTA hematology tubes (processing as soon as possible, <1 hour).

II. Further Processing

a. Buffy Coat isolation per BPM Core standard protocol, and store at -80°C as usual.

III. Kit contents

1. Four barcoded labels for 10 mL purple top EDTA hematology tubes
2. Four to 6 externally threaded cryovials with barcoded labels
3. Consent form

Appendix V Patient Diary for LY3023414 administration and Treatment Side Effects

Patient Diary

Patient: _____

Dates: _____ **to** _____

LY3023414 should be taken twice a day, about 12 hours apart, every day. LY3023414 should be taken with food, although it is not required. You should take your study drug at about the same times each day, and not take more than what is prescribed. You must swallow the study drug whole and not chew it or open the capsule before swallowing. Keep out of reach of children and do not give to any other person. Store the bottle within the temperature range stated on the label.

When you take your study medication, write the date and time taken in each of the corresponding boxes. If you miss a dose of LY3023414, you should take the dose as soon as possible, but not less than 6 hours before the next dose is due. If the next dose is due within 6 hours, you should skip the missed dose and take the next dose as scheduled. Put an "X" in the appropriate boxes on a day that you did not take LY3023414 (missed dose). **TAKE YOUR NEXT DOSE AT THE NEXT SCHEDULED TIME.**

Please remember to bring the medication bottles and any remaining medication with you to your next study visit or as instructed by the study staff. Please also bring this diary.

On the second page, please record any side effect you think you may be having during treatment. Please show this diary to your study coordinator at each visit.

Dosing Diary:

Day of the Week:							
Date:	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
LY3023414 Dose:	mg	mg	mg	mg	mg	mg	mg
Dose Times AM							
PM							

Day of the Week:							
Date:	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___	___/___/___
LY3023414 Dose:	mg	mg	mg	mg	mg	mg	mg
Dose Times AM							
PM							

Side Effects Diary:

1 Nausea
2 Vomiting
3 Diarrhea
4 Fatigue
5 Loss of Appetite
6 Rash
7 Mouth Sores
8 Constipation
9 Other (specify)

Side Effects	Day	Time(s)	Treatment	Time Taken	Result