Protocol I3Y-MC-JPBZ(f)

A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

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Approval date: 26-Feb-2021

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monarcHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

Abemaciclib (LY2835219)

This is a randomized, multicenter, 3-arm, open-label Phase 2 study to compare the efficacy of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy plus trastuzumab in women with HR+, HER2+ locally advanced or metastatic breast cancer.

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Protocol Electronically Signed and Approved by Lilly on 05 October 2015
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Approval Date: 26-Feb-2021 GMT

2. Synopsis

Study Rationale

The overexpression of the human epidermal growth factor receptor 2 (HER2) is associated with a poor prognosis in hormone-receptor-positive (HR+) metastatic breast cancer (mBC) patients. Although HER2-targeted therapies such as trastuzumab have improved clinical outcomes in this patient population, resistance often emerges to these therapies, and HER2 positive (HER2+), HR+ mBC remains an incurable disease. In preclinical models of resistance to a HER2-targeted agent, sustained cyclin D expression causes inappropriate activation of cyclin-dependent kinase (CDK) 4, which drives cancer cell growth. Inhibition of cyclin D/CDK 4 was able to overcome this mechanism of resistance. Abemaciclib (LY2835219) is a selective and potent small molecule inhibitor of CDK 4 and CDK 6 with antitumor activity in multiple preclinical pharmacology models and an acceptable toxicity profile in nonclinical species. Cell-based studies across a diverse panel of cell lines representing the known molecular subgroups of breast cancer indicated that sensitivity to the antiproliferative activity of abemaciclib is greater in HR+ cell lines (including HER2+ and HER2 negative [HER2-] cell lines). Clinically, abemaciclib has demonstrated evidence of single-agent activity in women with HR+ mBC (both HER2+ and HER2-) in the Phase 1 Study I3Y-MC-JPBA (JPBA). In this same study, abemaciclib demonstrated a clinically manageable safety profile for women with HR+ mBC. Preliminary safety data from Study I3Y-MC-JPBH of abemaciclib in combination with endocrine therapies in HR+ mBC patients are consistent with the safety profile from Study JPBA.

The evaluation of abemaciclib in combination with trastuzumab is of interest since CDK 4 inhibition may enhance the response to HER2-targeted therapy and could delay or overcome resistance. Study I3Y-MC-JPBZ is a randomized, multicenter, 3-arm, open-label phase 2 study to compare the efficacy of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy plus trastuzumab in women with HR+, HER2+ locally advanced or metastatic breast cancer.

Clinical Protocol Synopsis: Study I3Y-MC-JPBZ

Name of Investigational Product: Abemaciclib (LY2835219)	
Title of Study: monarcHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer	
Number of Planned Patients: Entered: 275 Enrolled/Randomized: 225 Completed: 225	**Phase of Development: 2**
Length of Study: approximately 48 months Planned first patient visit: Apr 2016 Planned last patient visit: Apr 2020	
Objectives: The primary objective of this study is to compare the efficacy of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab with respect to progression free survival (PFS). The secondary objectives of the study are to compare the 3 arms with respect to each of the following: • overall survival (OS) rate at 1, 2, and 3 years • objective response rate (ORR) • duration of response (DoR) (Complete response [CR] + partial response [PR]) • disease control rate (DCR) (CR + PR + stable disease [SD]) • clinical benefit rate (CBR) (CR + PR + SD ≥6 months) • safety and tolerability of abemaciclib in combination with trastuzumab and fulvestrant • impact on pain, disease symptoms, and overall quality of life using the modified Brief Pain Inventory-Short Form (mBPI-sf), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and the health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L) • pharmacokinetics (PK) of abemaciclib and its metabolites, fulvestrant, and trastuzumab in the target patient population • relationship between abemaciclib, trastuzumab, and fulvestrant exposure and response for safety and efficacy endpoints The exploratory objectives of this study are: • to explore potential biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of breast cancer and association with clinical outcome	
Study Design: Study I3Y-MC-JPBZ is a randomized, multicenter, 3-arm, open-label Phase 2 study to compare the efficacy of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab in women with HR+, HER2+ locally advanced or metastatic breast cancer	

Diagnosis and Main Criteria for Inclusion and Exclusions: Patients are eligible to be included in the study only if they meet all of the following criteria: [1] have a diagnosis of HR+, HER2+ advanced breast cancer ; [2] have unresectable locally advanced recurrent breast cancer or metastatic breast cancer ; [3] have adequate tumor tissue (newly obtained biopsy; otherwise archived tissue) available prior to randomization; [4] have measurable and/or non-measurable disease according to RECIST version 1.1; [5] have previously received at least 2 HER2-directed therapies for advanced disease and must have received T-DM1 in any disease setting; [6] must have received a taxane in any disease setting; [7] may have received any endocrine therapy (excluding fulvestrant); [8] have postmenopausal status due to either surgical/natural menopause or induced by ovarian suppression; [9] have a performance status (PS) of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale; [10] must have left ventricular ejection fraction (LVEF) of 50% or higher at baseline; [11] have adequate organ function; [12] have a negative serum pregnancy test at baseline and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression; [13] have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy; [14] have discontinued all previous therapies for cancer, except trastuzumab, for at least 21 days for myelosuppressive agents or 14 days for non-myelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy except for residual alopecia and peripheral neuropathy; [15] are female and ≥18 years of age; [16] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures; [17] have given written informed consent prior to any study-specific procedures; and [18] are able to swallow capsules.

Patients will be excluded from the study if they meet any of the following criteria: [19] have visceral crisis; [20] have known central nervous system (CNS) metastases that are untreated, symptomatic, or require steroids to control symptoms; [21] have had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound and site(s); [22] have received prior treatment with any CDK 4 and CDK 6 inhibitor; [23] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a non-myelosuppressive or myelosuppressive agent, respectively; [24] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study; [25] have a history within the last 6 months of symptomatic congestive heart failure, myocardial infarction, or unstable angina; [26] have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest; [27] have a history of any other cancer, unless in complete remission with no therapy for a minimum of 3 years. For patients with history of other cancers within 3 years and considered of very low risk of recurrence per investigator's judgment, eligibility is to be discussed with Lilly clinical research physician (CRP); [28] have active bacterial infection, fungal infection, or detectable viral infection; [29] have received any recent live virus vaccination; [30] are currently enrolled in a clinical trial involving an investigational product or non-approved use of a drug or, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study; or [31] hypersensitivity to trastuzumab, murine proteins, fulvestrant, or to any of the excipients.

Test Product, Dosage, and Mode of Administration: Abemaciclib will be supplied by the sponsor to be administered orally, 150 mg every 12 hours on Days 1 to 21 of a 21-day cycle. Trastuzumab 8 mg/kg will be administered as an intravenous (IV) infusion on Day 1 of Cycle 1 (21 day cycle) then 6 mg/kg IV infusion on Day 1 of each subsequent 21-day cycle. Fulvestrant 500 mg will be administered intramuscularly (IM) on Days 1, 15, and 29 (that is, Cycle 2 Day 8 [assuming no dose suspension for trastuzumab]), and once every 4 weeks thereafter.

Reference Therapy, Dose, and Mode of Administration: Standard-of-care single-agent chemotherapy of physician's choice will be administered according to product label.

Planned Duration of Treatment: until disease progression or other discontinuation criteria are fulfilled
Short-term follow-up (postdiscontinuation): 30 days
Long-term follow-up (postdiscontinuation): until death

Criteria for Evaluation:

Efficacy:

- PFS
- OS
- ORR
- DoR
- DCR
- CBR

Safety:

- Adverse events using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

Health Outcomes:

- mBPI-sf, EORTC QLQ-C30: assess impact on pain, disease symptoms, and overall quality of life
- EQ-5D 5L: describe health status changes

Pharmacokinetics/Pharmacodynamics:

- Population PK parameters for abemaciclib and its metabolites, fulvestrant, and trastuzumab
- Relationship between exposure and response, PFS, and toxicity (for example, diarrhea, neutropenia)

Biomarkers:

- Biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of breast cancer and association with clinical outcome

Statistical Methods:

Statistical:

The primary objective of this study is to compare abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab in terms of PFS in patients with advanced breast cancer. The primary analysis will be performed after approximately 165 PFS events have occurred. Assuming a hazard ratio of 0.667, this sample size yields at least 80% statistical power to detect superiority of the abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab arms over standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab arm with the use of an experiment-wise 1-sided alpha level of .10. An interim analysis of PFS for futility is planned by an assessment committee (AC) after 75 PFS events have been observed. Overall survival, an important secondary endpoint for this study, will be tested only if the test of PFS is significant. Up to a total of 2 interim analyses and a final analysis for OS may be performed, comparing the 2 pooled abemaciclib arms against the chemotherapy arm (at the time of PFS analysis, after approximately 105 deaths, and after approximately 158 deaths). The type I experiment-wise error rate will be controlled at 10% by using the Lan-Demets method with an O'Brien-Fleming like α-spending function.

Efficacy:

The PFS and OS analyses to test the superiority of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to chemotherapy plus trastuzumab in improving PFS time will use the log-rank test stratified by the stratification variable. Additional analyses will be performed using the Kaplan-Meier method to estimate the PFS and OS curves and rates, and the Cox proportional hazard model will be used to estimate the PFS and OS hazard ratios and corresponding confidence intervals.

Safety:

All safety summaries and analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of study treatment. Patients will be grouped according to treatment received in Cycle 1. There are 2 planned interim analyses to evaluate the safety and tolerability of the combination of abemaciclib plus trastuzumab plus fulvestrant in patients enrolled to the safety lead-in for Part A; these analyses will take place when data from the first 6 and 12 qualified patients who complete 1 cycle have been obtained. For all treatment arms in Study JPBZ, additional interim safety analyses are planned by an AC after approximately 36, 75, and 150 patients overall (a minimum of 12, 25, and 50 patients in the abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab arms) have received 1 cycle of study treatment to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment.

Health Outcomes:

Change in pain, symptom burden, and health status will be analyzed descriptively and treatment arms will be compared using a repeated measures model, where appropriate.

Pharmacokinetics/Pharmacodynamics:

Pharmacokinetic parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effect modeling implemented in nonlinear mixed effects modelling (NONMEM). If warranted by the data, PK parameters for abemaciclib metabolites, fulvestrant, or trastuzumab in plasma and inter-individual variability estimates will also be computed using nonlinear mixed-effect modeling implemented in NONMEM.

Biomarkers:

Correlative analyses will be performed to investigate associations between biomarkers and clinical endpoints.

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4. Abbreviations and Definitions

Term	Definition
AC	Assessment Committee
AE	adverse event Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BPI-sf	Brief Pain Inventory-short form
CAP	chest/abdomen/pelvis
CDK	cyclin-dependent kinase
CI	confidence interval
collection database	A computer database where clinical trial data are entered and validated.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
continued access period	The period between study completion and end of trial during which patients on study treatment who continue to experience clinical benefit and no undue risks may continue to receive study treatment until one of the criteria for discontinuation is met.
CNS	central nervous system
CR	complete response

CRF/eCRF	case report form/electronic case report form Sometimes referred to as clinical report form: A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
CRP	clinical research physician Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
IDMC	independent data monitoring committee
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
end of trial	End of trial is the date of the last visit or last scheduled procedure for the last patient.
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D 5L	EuroQOL 5 Dimension 5 Level
ERB/IRB	ethical review board/institutional review board A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical trial are protected.
FSH	follicle-stimulating hormone
GCP	good clinical practice
GnRH	gonadotropin-releasing hormone
GPS	Global Patient Safety
HIV	human immunodeficiency virus

HR	hormone receptor
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ILD	interstitial lung disease
Informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	International Normalized Ratio
interim analysis	An interim analysis is an analysis of clinical trial data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product (IP)	A pharmaceutical form of an active ingredient substance or placebo being tested, or used as a reference, in a clinical trial.
investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
ITT	intention-to-treat The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
legal representative	An individual, judicial, or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the clinical study.
Lilly Safety System	Global safety database that tracks and reports serious adverse and spontaneous events occurring while using a drug/drug delivery system.
LLT	Lower Level Term
MATE	multidrug and toxin extrusion protein
MedDRA	Medical Dictionary for Regulatory Activities
mBC	metastatic breast cancer
MRI	magnetic resonance imaging

MUGA	multigated acquisition
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PS	performance status
PT	Preferred Term
QTc	corrected QT interval
randomize	the process of assigning patients to an experimental group on a random basis
RECIST	Response Evaluation Criteria in Solid Tumors
reporting database	A point-in-time copy of the collection database. The final reporting database is used to produce the analyses and output reports for interim or final analyses of data.
re-screen	to screen a patient who was previously declared a screen failure for the same study
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, diagnostic psychological tests, x-rays, blood draws)]. For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study.
screen failure	patient who does not meet one or more criteria required for participation in a trial
SD	stable disease
SOC	System Organ Class

SPC	Summary of Product Characteristics
Study completion	This study will be considered complete after final evaluation of overall survival is performed.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin
TEAE	treatment-emergent adverse event Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.
TPO	third-party organization
ULN	upper limits of normal
VAS	visual analog scale
VTE	venous thromboembolic event

monarcHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

5. Introduction

Breast cancer is one of the most common cancers in women in the Unites States and Europe and is a leading cause of cancer death in women worldwide (Jemal et al. 2011). Early stage disease is treatable, but metastatic breast cancer (mBC) has a median overall survival (OS) of only 2 to 3 years (Cardoso et al. 2012). Overexpression of human epidermal growth factor receptor 2 (HER2) occurs in 20% to 25% of breast cancers with approximately half of these tumors also expressing hormone receptors (HR) (Konecny et al. 2003). Clinical studies have demonstrated that cyclin D is overexpressed in more than 50% of breast cancers, the majority of which are also estrogen receptor positive (ER+) (Velasco-Velazeques et al. 2011). While women who have been diagnosed with hormone receptor positive (HR+) mBC are typically treated with endocrine therapy, de novo or acquired resistance to endocrine therapy is a common clinical problem in this population.

Patients with HER2 positive (HER2+) breast cancers have tumors with higher proliferation rates, their metastases show greater predilection to metastasize to the brain and internal organs, and their clinical outcomes are worse when treated without concomitant HER2-targeted therapy.

Fortunately, HER2 may be targeted therapeutically by the monoclonal antibody trastuzumab and the small molecule inhibitor lapatinib. Recent advances have extended these treatment options to include the dimerization inhibitor pertuzumab and the antibody conjugate trastuzumab emtansine (T-DM1) (Kümler et al. 2014). Unfortunately, multiple mechanisms of resistance are known to emerge to these HER2-targeted therapies, notably those mediated by effectors downstream of the HER2 receptor (Thery et al. 2014). Per international guidelines, patients whose tumors progress on an anti-HER2 therapy in combination with a cytotoxic or endocrine agent should be offered additional anti-HER2 therapy with subsequent treatment because it is beneficial to continue suppression of the HER2 pathway (Cardoso et al. 2014).

Mitogenic signaling by the HER family of receptors engages the cell cycle machinery to promote cell division via cyclin D/cyclin-dependent kinase (CDK) 4 complexes (Witkiewicz et al. 2014). In preclinical models, pharmacologic inhibition of CDK 4 has demonstrated efficacy in HER2+ breast cancer explants and enhances activity of HER2-targeted therapy (Witkiewicz et al. 2014).

Abemaciclib (LY2835219) is a selective and potent small-molecule inhibitor of CDK 4 and CDK 6 with acceptable physical characteristics, pharmacokinetic (PK) properties, and safety profile in nonclinical species. Cell-based studies in breast cancer models have confirmed and demonstrated that abemaciclib inhibits CDK 4 and CDK 6 to induce G1 arrest specifically in cell

lines with intact retinoblastoma (Rb) tumor suppressor function (Rb+) versus lines which lack functional Rb (Rb-). These studies, which evaluated in vitro growth inhibition across a diverse panel of cell lines representing the known molecular subgroups of breast cancer, indicated that sensitivity to CDK 4 and CDK 6 inhibition was greater in hormone receptor positive (HR+) lines with luminal histology including a subset of those that are HER2+/ER+. Abemaciclib also shows antitumor activity in additional nonclinical models of multiple human cancers including, but not limited to, colorectal cancer, glioblastoma multiforme, acute myeloid leukemia, non-small cell lung cancer, and mantle cell lymphoma. Preclinical data have demonstrated that abemaciclib crosses the blood brain barrier and inhibits glioblastoma intracranial-xenografts in a dose-dependent manner (Sanchez-Martinez et al. 2011).

In the ongoing Phase 1 Study I3Y-MC-JPBA (JPBA), the maximum tolerated dose for single-agent abemaciclib was established at 200 mg every 12 hours. In Study JPBA, abemaciclib monotherapy has demonstrated a clinically manageable safety profile across 6 tumor-expansion cohorts, with the most common treatment-emergent adverse events (TEAEs) possibly related to study drug including diarrhea, nausea, fatigue, vomiting, and neutropenia. The safety and tolerability of continual twice-daily oral dosing of abemaciclib in combination with trastuzumab administered as an intravenous (IV) infusion on Day 1 of a 21-day cycle is being evaluated in patients with HER2+ mBC in the ongoing Phase 1b study, I3Y-MC-JPBH (JPBH). Preliminary safety data from Study JPBH have shown an adverse event (AE) profile for abemaciclib administered at 200 mg every 12 hours in combination with endocrine therapies that is consistent with the profile observed in the Study JPBA mBC single-agent cohort. However, at the 200-mg dose the incidence of treatment-emergent Grade 3 diarrhea was greater in combination with endocrine therapies than when abemaciclib was administered alone (25.7% and 13.6%, respectively). Clinical and PK findings from the single-agent Study JPBA and preliminary safety data from the abemaciclib/non-steroidal aromatase inhibitor (NSAI) combination in Study JPBH support 150 mg every 12 hours as the recommended dose for abemaciclib in combination with endocrine therapy in Study I3Y-MC-JPBZ (JPBZ).

Importantly, abemaciclib has demonstrated evidence of clinical activity in women with HR+ mBC (both HER2+ and HER2 negative [HER2-]) at doses of both 150 mg and 200 mg every 12 hours. In the ongoing Study JPBA, 47 patients in a tumor-specific cohort of women with mBC with a median of 7 prior systemic regimens received abemaciclib monotherapy. Among the 36 patients with HR+ mBC, the median progression-free survival (PFS) was 8.8 months and there were 12 confirmed partial responses (PR) for an objective response rate of 33.3%. The disease control rate (DCR) for patients with HR+ mBC was 80.6%. Among responder patients, 4 had HR+, HER2+ disease (36%). Collectively, these results support clinical development of abemaciclib in combination with HER2 targeted therapies for patients with HER2+ breast cancers.

More information about the known and expected benefits, risks and reasonably anticipated adverse events (AEs) of abemaciclib may be found in the Investigator's Brochure (IB). Information on AEs expected to be related to abemaciclib may be found in Section 7 (Development Core Safety Information) of the IB. Information on serious adverse events (SAEs) expected in the study population independent of drug exposure and that will be assessed

by the sponsor in aggregate, periodically during the course of the study, may be found in Section 6 (Effects in Humans) of the IB.

More detailed information about the known and expected benefits and risks of trastuzumab, fulvestrant, and single-agent chemotherapy may be found in the following: Patient Information Leaflet, Package Insert, or Summary of Product Characteristics (SPC).

5.1. Rationale for Amendment (a)

The Study JPBZ protocol was amended to incorporate a safety lead-in for Arm A (abemaciclib, trastuzumab, and fulvestrant) to monitor the safety and tolerability of the 3-drug combination. Although the 3 drugs have been shown to be tolerated individually at the doses specified for Study JPBZ, and 150-mg abemaciclib has demonstrated tolerability when combined as a doublet with trastuzumab or fulvestrant, there is no experience with the combination of all 3 drugs in humans. If the triplet combination is not tolerated, the starting dose of abemaciclib will be lowered to 100 mg. If the 100-mg dose is not tolerated, Arm A will be stopped.

Further modifications along with minor typographical and formatting edits were made for clarity and consistency.

5.2. Rationale for Amendment (b)

The Study JPBZ protocol has been amended to provide guidance on monitoring of renal function in patients receiving abemaciclib based on continued learning from the ongoing abemaciclib clinical program. Testing for serum levels of cystatin C was added to the clinical laboratory tests required for the study to gain data regarding the impact of abemaciclib on cystatin C levels.

With amendment (b), an additional stratification factor has been added to the study, namely: status of disease (measurable vs. nonmeasurable). While most patients in this disease setting are expected to present with visceral lesions that are measurable in a majority of cases, this additional stratification factor was necessary to ensure that randomization is balanced between treatment arms for the status of disease.

Abemaciclib suspension during the palliative radiotherapy period has been made mandatory regardless of the radiation target volume, in the absence of safety data for abemaciclib in concurrent combination with radiotherapy.

The protocol has also been amended to delete the analysis for time to worsening of pain, as this analysis should be considered exploratory and may be addressed in a separate Health Outcomes statistical analysis plan (SAP).

Consistent with requests from competent authorities in Europe (Agence Nationale de Sécurité du Médicament et des Produits de Santé and the Medicines and Healthcare Products Regulatory Agency), Exclusion Criterion [24] for preexisting conditions was updated to included severe dyspnea at rest or requiring oxygen therapy to align with the European trastuzumab label and to exclude patients with interstitial lung disease since prior exposure to taxanes is mandatory for all patients. Exclusion Criterion [29] has been clarified further with regard to prior exposure to live virus vaccines, and Exclusion Criterion [31] has been added to align with both the trastuzumab

and fulvestrant labels. In addition, the multigated acquisition (MUGA) scan and echocardiography schedule has been revised for consistency with the trastuzumab label. The protocol was also amended to reference the product label for guidance regarding the management of patients receiving trastuzumab and standard-of-care chemotherapy.

A typographical error in instructions for fulvestrant administration during the second cycle has been corrected and clarification of the maximum time interval between randomization and Cycle 1 Day 1 has been added. The protocol was also amended to clarify the tumor assessment guidance for patients with bone lesions. Additional revisions were made to the hepatic monitoring criteria to align with current guidance from the Lilly Liver and Gastrointestinal (GI) Safety Advisory Committee. Changes were made to the specified confidence intervals in the statistical and analytical plans to align with standard reporting.

Minor typographical and formatting edits were made for clarity and consistency.

5.3. Rationale for Amendment (c)

Study JPBZ protocol was amended to update the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients and align with the updated label of abemaciclib. Changes to the dose adjustment and delay section and Table JPBZ.9.2 were done to specify dose modifications in response to Grade 2 diarrhea and increased alanine aminotransferase laboratory values.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.4. Rationale for Amendment (d)

Study JPBZ protocol was amended to update the dose modification guidance and the safety language for interstitial lung disease (ILD)/pneumonitis. Changes to the dose adjustment and delay section and to Table JPBZ.9.2 were made to include dose modifications in response to ILD/pneumonitis events. These updates are in alignment with changes made in the development core safety information of the IB.

Section 9.6 (Concomitant Therapy) was updated to align with the current IB. Additional language was added cautioning against concomitant use of abemaciclib and substrates of the following:

- P-glycoprotein
- breast cancer resistance protein
- organic cation transporter 2
- multidrug and toxin extrusion protein 1 (MATE1), and
- MATE2-K

Substrates of these transporters, including metformin, digoxin, and dofetilide, should be substituted or avoided.

The Concomitant Therapy (Section 9.6) was also updated to remove cautionary language regarding coadministration of narrow therapeutic index cytochrome P450 (CYP) substrate drugs. This is based on a clinical study (Study I3Y-MC-JPCB) which found no meaningful effect of abemaciclib on the PK of CYP substrates, namely

- caffeine (CYP1A2)
- S-warfarin (CYP2C9)
- midazolam (CYP3A), and
- dextromethorphan [CYP2D6]).

The list of inducers and strong inhibitors of CYP3A (Attachment 9) was also modified to reflect updated guidance.

The protocol was updated to bring references to abemaciclib into alignment with the sponsor's standard language.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.5. Rationale for Amendment (e)

This amendment to the Study JPBZ protocol updates the dose adjustment guidance related to nonhematologic toxicity, ALT/AST increased, and VTEs. Specifically, dose adjustment updates were made in Table JPBZ.9.2 to ensure alignment with the current IB. Additionally, the Concomitant Therapy (Section 9.6) information was updated for CYP3A modulators and transporter substrates. Finally, safety monitoring language in Special Hepatic Safety Data Collection (Section 10.3.3.1) and Venous Thromboembolic Events (Section 10.3.3.3) was updated to align with current guidance and the IB, respectively.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

5.6. Rationale for Amendment (f)

This amendment to the Study JPBZ protocol corrects an error in the table in Special Hepatic Safety Data Collection (Section 10.3.3.1) to align with current guidance.

6. Objectives

6.1. Primary Objective

The primary objective of this study is to compare the efficacy of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab with respect to progression free survival (PFS).

6.2. Secondary Objectives

The secondary objectives of the study are to compare the 3 arms with respect to each of the following:

- overall survival (OS) rate at 1, 2, and 3 years
- objective response rate (ORR)
- duration of response (DoR) (Complete response [CR] + partial response [PR])
- disease control rate (DCR) (CR + PR + stable disease [SD])
- clinical benefit rate (CBR) (CR + PR + SD ≥6 months)
- safety and tolerability of abemaciclib in combination with trastuzumab and fulvestrant
- impact on pain, disease symptoms, and overall quality of life using the modified Brief Pain Inventory-Short Form (mBPI-sf), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and the health status scores from the EuroQol 5-Dimension 5 Level (EQ-5D 5L)
- PK of abemaciclib and its metabolites, fulvestrant, and trastuzumab in the target patient population
- relationship between abemaciclib, trastuzumab, and fulvestrant exposure and response for safety and efficacy endpoints

6.3. Exploratory Objectives

- to explore potential biomarkers related to the mechanism of action of abemaciclib, the cell cycle, and/or the pathogenesis of breast cancer and their association with clinical outcome

7. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened (Section 7.2.1).

Study participants should be instructed not to donate blood or blood products during the study or for 2 weeks following the last dose of study drug.

Prospective approval of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) is not permitted.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] have a diagnosis of HR+, HER2+ advanced breast cancer

- To fulfill the requirement of HR+ disease, the primary tumor or metastatic lesion of the breast cancer must express at least one of the hormone receptors (estrogen receptor [ER] or progesterone receptor [PgR]) by immunohistochemistry (IHC). Estrogen receptor and PgR assays are considered positive if there are at least 1% positive tumor nuclei in the sample as defined in the relevant American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Guidelines (Hammond et al. 2010).
- To fulfill the requirement of HER2+ disease, the primary tumor or metastatic lesion of the breast cancer must demonstrate overexpression of HER2 by either IHC (3+) or gene amplification by positive in-situ hybridization (ISH) as defined in the relevant ASCO/CAP HER2 guidelines (Wolff et al. 2013).

Although not required as a protocol procedure, a patient with a new metastatic lesion should be considered for fresh biopsy (whenever possible) to reassess HR and HER2 status prior to study entry if clinically indicated. The most recent receptor testing should be used to determine eligibility.

[2] have unresectable locally advanced recurrent breast cancer or metastatic breast cancer (all termed advanced disease)

[3] have adequate tumor tissue (newly obtained biopsy; otherwise archived tissue) available prior to randomization.

Note: Sites should confirm the availability of adequate tumor tissue (Section 10.4.2.2.2) with the pathological laboratory prior to randomization.

[4] have measurable and/or non-measurable disease according to RECIST version 1.1 (Eisenhauer et al. 2009)

[5] have previously received:

- at least 2 HER2-directed therapies for advanced disease
  - prior HER2-directed therapies could be in combination with chemotherapy or endocrine therapy or as single agent
  - exposure to dual HER2 blockade (for example, combination trastuzumab and pertuzumab) is considered as 1 prior HER2-directed therapy
- patient must have received T-DM1 in any disease setting
- prior trastuzumab and/or pertuzumab and/or lapatinib are allowed in any disease setting

[6] patient must have received a taxane in any disease setting

[7] patients may have received any endocrine therapy (excluding fulvestrant)

[8] have postmenopausal status due to either surgical/natural menopause or chemical ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin or radiation-induced ovarian suppression

- postmenopausal status due to surgical/natural menopause is defined as meeting one of the following conditions:
  - prior bilateral oophorectomy
  - age ≥60 years
  - age <60 years and amenorrheic (in the absence of tamoxifen, toremifene, ovarian suppression, or chemotherapy) for at least 12 months. Follicle-stimulating hormone (FSH) and estradiol must be in the postmenopausal range.
- Postmenopausal status due to radiation-induced ovarian suppression must be confirmed by FSH and estradiol level in the postmenopausal range

[9] have a performance status (PS) of 0 to 1 on the Eastern Cooperative Oncology Group (ECOG) scale (see Attachment 4)

[10] must have left ventricular ejection fraction (LVEF) of 50% or higher at baseline (determined by echocardiography or multiple-gated acquisition scanning)

[11] have adequate organ function, including:

- hematologic: absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, and hemoglobin ≥8 g/dL. Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.

- hepatic: total bilirubin ≤1.5 × the upper limit of normal (ULN) (except in cases of known Gilbert's syndrome where ≤ 2.0x ULN is allowed) and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 × ULN. If liver metastases are present, AST and ALT ≤5 × ULN are acceptable.
- renal: serum creatinine ≤1.5 × ULN

[12] have a negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist or induced by radiation

[13] have discontinued previous localized radiotherapy for palliative purposes or for lytic lesions at risk of fracture at least 2 weeks prior to randomization and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy

[14] have discontinued all previous therapies for cancer (including chemotherapy, radiotherapy, immunotherapy, and endocrine therapy), except trastuzumab, for at least 21 days for myelosuppressive agents or 14 days for non-myelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at lease Grade 1) except for residual alopecia and peripheral neuropathy. See Table JPBZ.9.1 Footnote (a) for guidance regarding trastuzumab continuation at the time of study entry.

[15] are female and ≥18 years of age

[16] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[17] have given written informed consent prior to any study-specific procedures

[18] are able to swallow capsules

7.2. Exclusion Criteria

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

[19] have visceral crisis. Visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease.

[20] have known central nervous system (CNS) metastases that are untreated, symptomatic, or require steroids to control symptoms. Note: patients with a history of treated brain- metastases are eligible.

- treated brain-metastases are defined as those having no evidence of progression for ≥2 months and no ongoing requirement for corticosteroids, as ascertained by clinical examination and by brain imaging (magnetic resonance imaging [MRI] or computed tomography [CT]) during the screening period
- any corticosteroid use for brain metastases must have been discontinued without the subsequent appearance of symptoms for ≥2 weeks before randomization
- treatment for brain metastases may include whole brain radiation (WBRT), radiosurgery, or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection must be at least 8 weeks from surgery. A wash out period of at least 8 weeks is required after end of WBRT.

[21] have had major surgery within 14 days prior to randomization to allow for post-operative healing of the surgical wound and site(s). Note: A surgery is qualified as major per investigator/surgeon judgment based on the required recovery period, both from general patient status and post-operative healing perspectives.

[22] have received prior treatment with any CDK 4 and CDK 6 inhibitor (or participated in any CDK 4 and CDK 6 inhibitor clinical trial for which treatment assignment is still blinded)

[23] have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days of randomization for a non-myelosuppressive or myelosuppressive agent, respectively

[24] have serious preexisting medical conditions that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis)

[25] have a history within the last 6 months of symptomatic congestive heart failure, myocardial infarction, or unstable angina

[26] have a personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest

[27] have a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years. For patients with history of other cancers within 3 years and considered of very low risk of recurrence per investigator's judgment (for example, papillary thyroid cancer treated with surgery), eligibility is to be discussed with Lilly clinical research physician (CRP)

[28] have active bacterial infection (that is to say, requiring IV antibiotics at time of initiating study treatment), fungal infection, or detectable viral infection (for example, known human immunodeficiency virus [HIV] positivity or known active or inactive hepatitis carrier [for example, hepatitis B surface antigen (HBsAg) positive]). Screening is not required for enrollment.

[29] have received any recent (within 28 days prior to randomization) live virus vaccination

[30] are currently enrolled in a clinical trial involving investigational product (IP) or non-approved use of a drug or device (other than the IP/device used in this study), or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study

[31] hypersensitivity to trastuzumab, murine proteins, fulvestrant, or to any of the excipients

7.2.1. Rescreening

A patient who fails screening is allowed to screen again after signing a new informed consent form (ICF) and will be assigned a new patient number under the conditions specified in this section.

The following patients may be eligible for rescreening if any of the following circumstances:

- patients who have become eligible to enroll in the study as the result of a protocol amendment.
- patient status has changed such that the eligibility criterion that caused the patient to screen fail would no longer cause the patient to screen fail again.
- patients who complete screening and meet all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as, severe weather, death in family, child illness).

The investigator should contact the Lilly CRP prior to rescreening a patient.

7.3. Discontinuation

If a patient withdraws informed consent, she must not be contacted unless she has explicitly provided permission and consent. Lilly may continue to use previously collected medical research data prior to the withdrawal consistent with the original authorization.

7.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If the investigator site identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the sponsor must be notified. If the sponsor identifies a patient who did not meet enrollment criteria and who was inadvertently enrolled, the investigator site will be notified. A discussion must occur between the sponsor CRP and the investigator to determine whether the patient may continue in the study, with or without study treatment. Inadvertently enrolled patients may be maintained in the study and on study treatment when the Lilly CRP agrees with the investigator that it is medically

appropriate for that patient. The patient may not continue in the study with or without study treatment if the Lilly CRP does not agree with the investigator's determination it is medically appropriate for the patient to continue. The investigator must obtain documented approval from the Lilly CRP to allow the inadvertently enrolled patient to continue in the study with or without study treatment.

7.3.2. Discontinuation from Study Treatment and/or from Study

In addition, patients will be discontinued from the study drugs and/or from the study in the following circumstances:

- progressive disease (PD) as defined by RECIST v1.1
- an unacceptable AE and/or toxicity occurs (for example, a persistent moderate toxicity that is intolerable to the patient)
- enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- investigator decision
  - the investigator decides that the patient should be discontinued from the study or study treatment
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study treatment occurs prior to introduction of the new agent
- patient decision
  - the patient or the patient's designee (for example, legal guardian) requests to be withdrawn from the study or study treatment
- sponsor decision
- Lilly stops the study or stops the patient's participation in the study for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- patient is significantly non-compliant with study procedures and/or treatment

The reason and date of discontinuation will be collected for all patients. All enrolled patients who discontinue regardless of whether or not they received study drug will have procedures performed as shown in the Study Schedule (Attachment 1).

7.3.3. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, the investigator, or the ethical review board (ERB) of the study site judges discontinuation of study site participation necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

7.3.4. Discontinuation of the Study

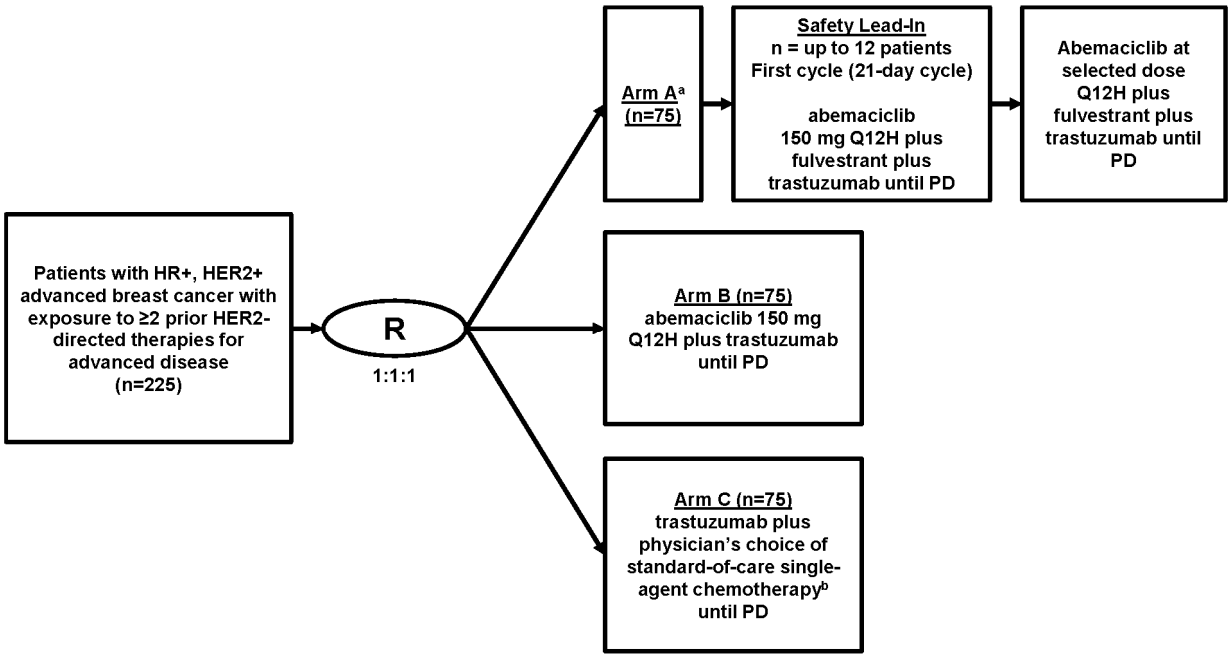
The study will be discontinued if Lilly judges discontinuation of the study necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP.

8. Investigational Plan

8.1. Summary of Study Design

Study I3Y-MC-JPBZ is a randomized, multicenter, 3-arm, open-label Phase 2 study to compare the efficacy of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab in women with HR+, HER2+ locally advanced or metastatic breast cancer.

Figure JPBZ.8.1 illustrates the study design.



Abbreviations: HER2+ = human epidermal growth factor receptor 2-positive; HR+ = hormone receptor-positive; n = number; PD = progressive disease; Q12H = every 12 hours; R = randomization.

[a] If the dose of abemaciclib in Arm A is reduced to 100 mg, patients that initiated treatment at the 150-mg dose will be dose-reduced to 100 mg, and patients who started at the 150-mg abemaciclib dose will be replaced so that there are a total of 75 patients in Arm A with a starting dose of 100-mg abemaciclib.

[b] Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

Figure JPBZ.8.1. Illustration of study design.

Approximately 225 patients will be randomized 1:1:1 between the 3 arms. Patients will be randomized using the following stratification factors: the number of previous systemic regimens (excluding single-agent endocrine therapy) for advanced breast cancer (2 to 3 vs. more than 3) and status of disease (measurable vs. nonmeasurable).

During enrollment into all 3 study arms, the first 12 patients enrolled to Arm A (abemaciclib plus trastuzumab plus fulvestrant) will be part of a safety lead-in. If the triplet combination is not tolerated, the starting dose of abemaciclib will be lowered to 100 mg. If the 100-mg dose is not tolerated, Arm A will be stopped. The interim analyses for the safety lead-in are described in detail in Section 12.2.12.

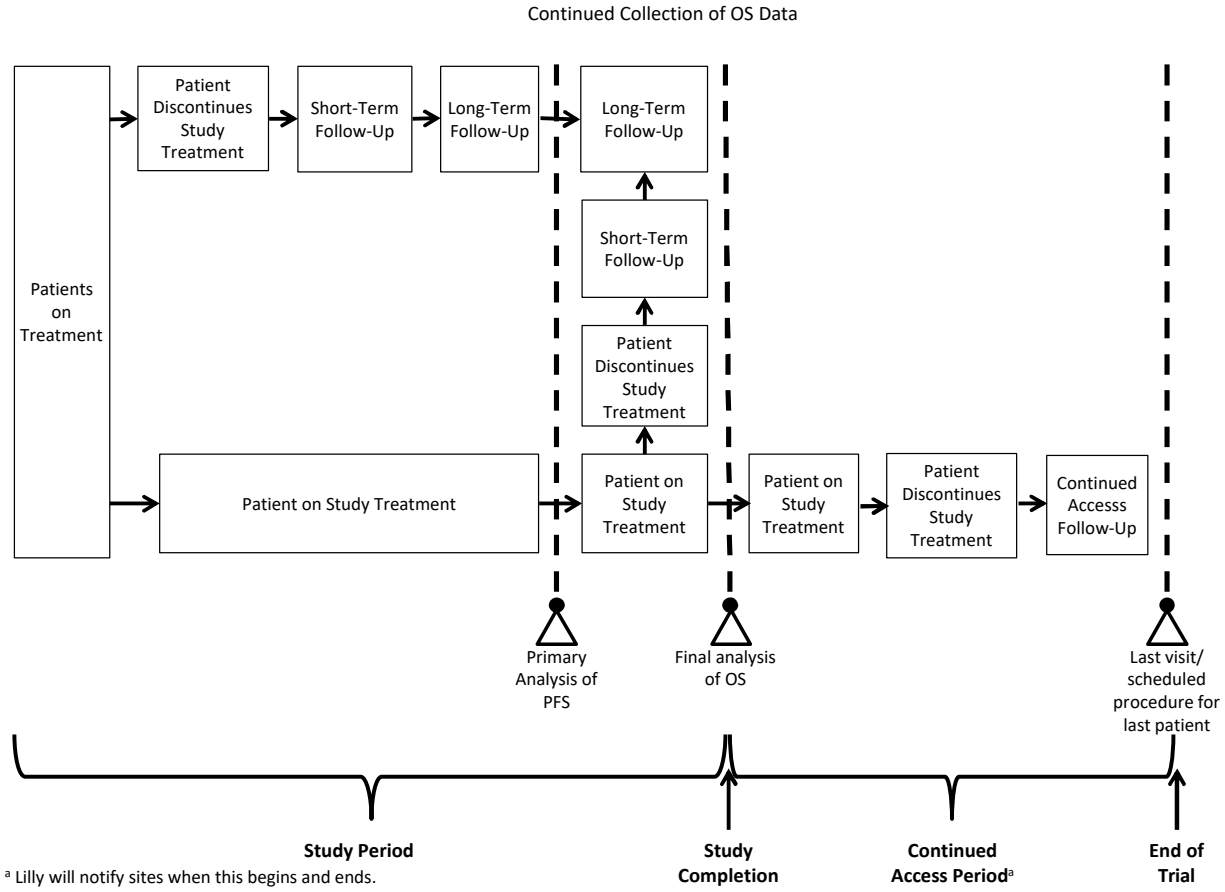
Terms used to describe the periods during the study are defined below:

- **Baseline:** begins when the ICF is signed and ends at the first study treatment dose (or at discontinuation, if no treatment is given). This may be up to 28 days prior to the first study treatment dose.
- **Study Period:** begins at the first study treatment dose and ends at study completion. The study period does not include the continued access period.
    - **Study Treatment Period:** begins at the first study treatment dose and ends when the patient and the investigator agree that the patient will no longer continue study treatment. This date is to be reported on the electronic case report form (eCRF) as the Date of Discontinuation from study treatment.
- **Postdiscontinuation Follow-Up:** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment.
    - ***Short-term follow-up*** begins the day after the patient and the investigator agree that the patient will no longer continue study treatment and lasts approximately 30 days.
    - ***Long-term follow-up*** begins the day after short-term follow-up is completed and continues until the patient's death or overall study completion.
- **Continued Access Period:** begins after study completion and ends at the end of trial. During the continued access period, patients on study treatment who continue to experience clinical benefit may continue to receive study treatment until one of the criteria for discontinuation is met.
    - The continued access period includes continued access period short-term follow-up.
    - Continued access short-term follow-up: begins the day after the patient and the investigator agree that the patient will no longer continue treatment in the continued access period and lasts approximately 30 days.

8.1.1. Study Completion and End of Trial

This study will be considered complete (that is, the scientific evaluation will be complete [study completion]) following the final evaluation of overall survival (refer to Figure JPBZ.8.2) as determined by Lilly. Investigators will continue to follow the study schedule for all patients until notified by Lilly that study completion has occurred. "End of trial" refers to the date of the last visit or last scheduled procedure for the last patient.

The end of trial occurs after study completion and after the last patient has discontinued study treatment and completed any applicable continued access follow-up (refer to Figure JPBZ.8.2).



Abbreviations: OS = overall survival; PFS = progression-free survival

Figure JPBZ.8.2. Study period and continued access diagram.

8.1.2. Continued Access Period

The continued access period will apply to this study only if at least 1 patient is still on study treatment when study completion occurs.

Patients receiving study treatment and experiencing ongoing clinical benefit and no undue risks may continue to receive study treatment in the continued access period until one of the criteria for discontinuation is met (Section 7.3). During the continued access period, crossover into another treatment arm will not be permitted. Lilly will notify investigators when the continued access period begins.

Patients who are in short-term follow-up when the continued access period begins will continue in short-term follow-up until the 30-day short-term follow-up visit is completed. Long-term follow-up does not apply.

Patients who are in long-term follow-up when the continued access period begins will be discontinued from long-term follow-up.

During the continued access period, all AEs, SAEs, and study treatment exposure will be reported on the eCRF. Serious adverse events will also be reported to Lilly Global Patient Safety (see Section 10.3.1). In the event that an SAE occurs, Lilly may request additional information (such as local laboratory results, concomitant medications, and hospitalizations) in order to evaluate the reported SAE.

Investigators will perform any other standard procedures and tests needed to treat and evaluate patients; however, the choice and timing of the tests will be at the investigator's discretion. Lilly will not routinely collect the results of these assessments.

8.2. Discussion of Design and Control

A randomized, controlled design is being used in this study. Randomization minimizes systematic bias in the selection and assignment of patients to study treatment and provides justification for inferential statistical methods to be used on data from this study. Using an appropriate concurrent control arm enables direct statistical estimation of benefits and harms due to study treatment and minimizes bias in the assessment and interpretation of observed treatment effects. Patients will be stratified for differences in factors thought to be associated with clinical outcomes to further reduce the potential for bias and improve the power of the analyses.

9. Treatment

9.1. Treatments Administered

The following treatments will be administered in this study:

- Experimental Arm A: abemaciclib 150 mg orally Q12H on Days 1 to 21 of a 21-day cycle; plus trastuzumab 8 mg/kg IV infusion on Day 1 of Cycle 1 (21-day cycle) then 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent 21-day cycle; plus fulvestrant 500 mg intramuscularly (IM) on Days 1, 15, and 29 (that is, Cycle 2 Day 8 [assuming no dose suspension for trastuzumab]), and once every 4 weeks thereafter (see Attachment 8). If this combination is not tolerated during the safety lead-in period, the abemaciclib dose in this arm will be reduced to 100 mg.
- Experimental Arm B: abemaciclib 150 mg orally Q12H on Days 1 to 21 of a 21-day cycle plus trastuzumab 8 mg/kg IV infusion on Day 1 of Cycle 1 (21-day cycle) then 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent 21-day cycle
- Control Arm C: trastuzumab as 8 mg/kg IV infusion on Day 1 of Cycle 1 (21-day cycle) then 6 mg/kg IV infusion on Day 1 of each subsequent 21-day cycle plus standard-of-care single-agent chemotherapy of physician's choice administered according to product label

Patients will receive study treatment in the assigned treatment arm until they meet any of the discontinuation criteria (see Section 7.3).

Table JPBZ.9.1 shows the treatment regimens.

Table JPBZ.9.1. Treatment Regimens/Dosing Schedule

Regimen	Cycle Length	Drug	Dose
Experimental Arm A	21-day cycle	abemaciclib	The starting dose of abemaciclib will be determined based on the results of the safety lead-in; 150 mg PO Q12H dose **or** 100 mg PO Q12H dose if the 150-mg dose is declared not tolerable.
		trastuzumab	8 mg/kg loading dose[a] IV infusion over 90 min on Day 1 of Cycle 1, then 6 mg/kg maintenance dose[b] on Day 1 of all subsequent cycles (see Section 9.1.1.2)
		fulvestrant[c]	500 mg IM on Days 1, 15, and 29 (that is, Cycle 2 Day 8 [assuming no dose suspension for trastuzumab]), and once every 4 weeks thereafter (see Attachment 8)
Experimental Arm B	21-day cycle	abemaciclib	150 mg PO Q12H dose
		trastuzumab	8 mg/kg loading dose[a] IV infusion over 90 min on Day 1 of Cycle 1, then 6 mg/kg maintenance dose[b] on Day 1 of all subsequent cycles (see Section 9.1.1.2)
Control Arm C	21-day cycle	trastuzumab	8 mg/kg loading dose[a] IV infusion over 90 min on Day 1 of Cycle 1, then 6 mg/kg maintenance dose[b] on Day 1 of all subsequent cycles (see Section 9.1.1.2)
		standard-of-care single-agent chemotherapy[d]	per label

Abbreviations: IM = intramuscular; IV = intravenous; min = minute; PO = orally; Q12H = every 12 hours.

[a] For patients already receiving trastuzumab at time of study entry (on a weekly or every-3-week basis), the trastuzumab dose on Cycle 1 Day 1 should be at least 21 days after the last dose administered. No loading dose of trastuzumab is required if the last dose of trastuzumab was within 4 weeks of Day 1 of Cycle 1. Loading dose of trastuzumab is required if the last dose of trastuzumab was administered more than 4 weeks prior to Day 1 of Cycle 1.

[b] If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

[c] Fulvestrant should be administered IM into the buttocks slowly (1 to 2 minutes per injection) as two 250-mg injections, one in each buttock; however, for patients with moderate hepatic impairment (defined as Child Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered intramuscularly into the buttock slowly (1 to 2 minutes) as one 250-mg injection. It is recommended that fulvestrant be administered after trastuzumab for the comfort of the patient who must be seated during trastuzumab infusion.

[d] Best supportive care alone, including palliative radiotherapy in the absence of chemotherapy, is not permitted. T-DM1 or pertuzumab are not considered a single-agent chemotherapy option. Maintenance endocrine therapy (except fulvestrant) after single-agent chemotherapy, all concurrently with trastuzumab, is allowed. Standard-of-care single-agent chemotherapy should include approved drug in breast cancer.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the drugs and planned duration of each individual's treatment to the patient/site personnel/legal representative,
- verifying that instructions are followed properly,

- maintaining accurate records of study treatment dispensing and collection,
- and returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study treatment so that the situation can be assessed.

9.1.1. Treatment Administration Guidance

9.1.1.1. Abemaciclib (Arms A and B)

Abemaciclib will be provided by the sponsor and dosed at 50 mg. Solid oral dosage units should be taken Q12H, at the same time each day with a glass of water. Swallow dosage units whole. Do not open, chew, or crush.

9.1.1.2. Trastuzumab (Arms A, B, and C)

The investigator should refer to the trastuzumab label (Patient Information Leaflet, Package Insert, or SPC). When locally sourced, it is important to check the vial labels to ensure that the drug being prepared and administered is Herceptin (trastuzumab) and not Kadcyla (trastuzumab emtansine) in order to prevent medication errors. Trastuzumab loading dose should be administered as a 90-minute IV infusion. Do not administer as an IV push or bolus. If the initial loading dose was well tolerated, the subsequent doses can be administered as a 30-minute infusion.

9.1.1.3. Fulvestrant (Arm A)

The investigator should refer to the fulvestrant label (Patient Information Leaflet, Package Insert, or SPC).

Due to the intramuscular route of administration, fulvestrant should be used with caution if treating patients with bleeding diatheses, thrombocytopenia or those taking anticoagulant treatment.

9.1.1.4. Standard-of-Care Chemotherapy (Arm C)

The investigator should refer to the product label for administration of standard-of-care single-agent chemotherapy of choice.

9.2. Materials and Supplies

Abemaciclib will be supplied by Lilly for oral administration. Abemaciclib should be stored according to the temperature range listed on the product label, and should not be opened, crushed, or chewed.

Fulvestrant will be centrally sourced by Lilly. Depending on country requirements, trastuzumab will be supplied by the site or centrally sourced by Lilly. Sites should confirm trastuzumab source to ensure adequate supply. Trastuzumab and fulvestrant should be stored according to the

instructions on the product label and administered according to the instructions in the protocol. Fulvestrant and trastuzumab, where supplied by Lilly, will be labeled according to the country's regulatory requirements.

Investigators should instruct patients to store study drugs in the original package provided and in a location inaccessible to children.

9.3. Method of Assignment to Treatment

Patients who meet all criteria for enrollment will be randomly assigned to receive abemaciclib plus trastuzumab plus fulvestrant, abemaciclib plus trastuzumab, or standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab at Visit 1. Randomization will be stratified by the number of previous systemic regimens (excluding single-agent endocrine therapy) for advanced breast cancer (2 to 3 vs. more than 3) and status of disease (measurable vs. nonmeasurable).

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS).

The period between randomization to study drug and the first dose (Cycle 1, Day 1) should not exceed 7 days.

9.4. Selection and Timing of Doses

A cycle is defined as an interval of 21 days.

Abemaciclib will be taken orally Q12H (± approximately 2 hours) on Days 1 through 21 of a 21-day cycle, for a total of 42 doses per cycle. Abemaciclib may be taken without regard to meals. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses (that is, dose is not taken within 2 hours of regularly scheduled dose) or vomits a dose, that dose should be omitted.

For patients already receiving trastuzumab at time of study entry, the trastuzumab dose on Cycle 1 Day 1 should be at least 21 days after the last dose administered prior to randomization. No loading dose of trastuzumab is required if the last dose of trastuzumab was within 4 weeks of Day 1 of Cycle 1. Loading dose of trastuzumab is required if the last dose of trastuzumab was administered more than 4 weeks prior to Day 1 of Cycle 1.

The timing of drug doses for each treatment arm is as follows (arms are described in Section 9.1):

- Arm A: Abemaciclib morning dose should be administered any time prior to trastuzumab infusion on Cycle 1 Day 1. After Cycle 1 Day 1, abemaciclib doses can be taken with no restriction relative to timing of trastuzumab infusion or fulvestrant dose. Fulvestrant is to be administered immediately after the end of trastuzumab infusion if trastuzumab is well tolerated.
- Arm B: Abemaciclib morning dose should be administered any time prior to trastuzumab infusion on Cycle 1 Day 1. After Cycle 1 Day 1, abemaciclib doses can be taken with no restriction relative to timing of trastuzumab infusion.
- Arm C: There are no restrictions relative to timing of trastuzumab and standard-of-care chemotherapy. Note that in trastuzumab clinical trials, chemotherapy is commonly administered immediately after trastuzumab infusion if trastuzumab was well tolerated.

In the event of a dose suspension of any study drug due to toxicity immediately prior to the beginning of a cycle, the PK Sampling Schedule may require adjustment. In these exceptional circumstances, the sponsor should be notified.

A patient may continue to receive study drug until she meets one or more of the specified reasons for discontinuation (as described in Section 7.3).

9.4.1. Special Treatment Considerations

9.4.1.1. Dose Adjustments and Delays

Table JPBZ.9.2 presents guidance for abemaciclib dose adjustments and delays due to toxicity.

Table JPBZ.9.2. Toxicity Dose Adjustments and Delays of Abemaciclib

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Hematologic Toxicity	Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2	Dose **MAY** be reduced by 1 dose level - investigator's discretion
Hematologic Toxicity	Recurrent Grade 3	Dose **MUST** be suspended until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by 1 dose level
Hematologic Toxicity	Grade 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by 1 dose level
Hematologic toxicity: If patient requires administration of blood cell growth factors (Section 9.6.3.3)	Regardless of severity (Use of growth factors according to ASCO Guidelines)	Dose **MUST** be suspended for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to at least Grade 2	Dose **MUST** be reduced by 1 dose level unless already performed for incidence of toxicity that lead to the use of growth factor
Nonhematologic Toxicity[b] (except diarrhea, ALT/AST increased, ILD/pneumonitis, and VTEs)	Persistent or recurrent Grade 2 that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1	Dose **MUST** be reduced by 1 dose level
Nonhematologic Toxicity[b] (except diarrhea, ALT/AST increased, ILD/pneumonitis, and VTEs)	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to either baseline or Grade 1	Dose **MUST** be reduced by 1 dose level
Diarrhea Section 9.6.3.1	Grade 2 that does not resolve within 24 hours to at least Grade 1	Dose **MUST** be suspended until toxicity resolves to at least Grade 1	Dose reduction is NOT required
Diarrhea Section 9.6.3.1	Persistent or recurrent[a] Grade 2 that does not resolve with maximal supportive measures, or any Grade of diarrhea that requires hospitalization	Dose **MUST** be suspended until toxicity resolves to at least Grade 1	Dose **MUST** be reduced by 1 dose level

Toxicity Type	Toxicity Profile and Severity	Dose Suspension	Dose Reduction
Diarrhea Section 9.6.3.1	Grade 3 or 4	Dose **MUST** be suspended until toxicity resolves to at least Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased Section 10.3.3.1	Persistent or recurrent[a] Grade 2 (>3.0-5.0×ULN)[d], or Grade 3 (>5.0-20.0×ULN)[c]	Dose **MUST** be suspended until toxicity resolves to baseline or Grade 1.	Dose **MUST** be reduced by 1 dose level.
ALT/AST Increased Section 10.3.3.1	Grade 4 (>20.0×ULN)	Abemaciclib therapy **MUST** be discontinued.	Abemaciclib therapy **MUST** be discontinued.
ALT/AST Increased with increased total bilirubin, in the absence of cholestasis	≥Grade 2 increased ALT/AST (>3.0 x ULN) with total bilirubin >2 x ULN	Abemaciclib therapy **MUST** be discontinued	Abemaciclib therapy **MUST** be discontinued
ILD/Pneumonitis Section 10.3.3.4	Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or Grade 1 within 7 days	Dose **MUST** be suspended until toxicity resolves to baseline or Grade ≤1	Dose **MUST** be reduced by 1 dose level.
ILD/Pneumonitis Section 10.3.3.4	Grade 3 or 4	Abemaciclib therapy **MUST** be discontinued	Abemaciclib therapy **MUST** be discontinued
VTEs Section 10.3.3.3	Grade 3 or 4	Suspend dose and treat as clinically indicated. May resume study drug when participant is clinically stable	Suspend dose and treat as clinically indicated. May resume study drug when participant is clinically stable

Abbreviations: ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; ILD = interstitial lung disease; VTE = venous thromboembolic event.

Note: MUST = mandatory.

a Determination of persistent events will be at the discretion of the investigator. Recurrent toxicity refers to the same event occurring within the next 6 weeks (as measured from the stop date of the preceding event). As a general guidance, based on the risk/benefit balance assessment per the investigator, for a patient who experiences a new episode of Grade 3 hematological toxicity after more than 6 weeks following the last episode of same Grade 3 hematological toxicity, the investigator may consider resuming the patient on the same drug dose should the patient satisfy the following conditions:

- shows stable hematological counts (Grade ≤2) during that timeframe
- has the absence of any infectious sign or risk factor
- is benefiting from study treatment

b Additional guidance for renal and hepatic monitoring is in Sections 10.3.3.1 and 10.3.3.2.

c Grade 3 ALT/AST increased is a trigger for additional assessments and possibly hepatic monitoring. See Section 10.3.3.1 for additional guidance for hepatic monitoring.

d The patient who presents with no liver metastases at baseline.

9.4.1.1.1. Dose Adjustments

9.4.1.1.1.1. Abemaciclib

Abemaciclib dose adjustments as outlined in Table JPBZ.9.3 are allowed both within a cycle and between cycles. Abemaciclib must be reduced sequentially by 1 dose level.

For patients requiring dose reduction(s), any re-escalation to a prior dose level is permitted only after consultation with the Lilly CRP. After re-escalation, subsequent dose adjustments should be based on the dose of abemaciclib that the patient is currently receiving.

Table JPBZ.9.3. Dose Adjustments for Abemaciclib

Dose Adjustment Level	Oral Dose	Frequency
0	150 mg	Every 12 hours
1	100 mg	Every 12 hours
2	50 mg	Every 12 hours

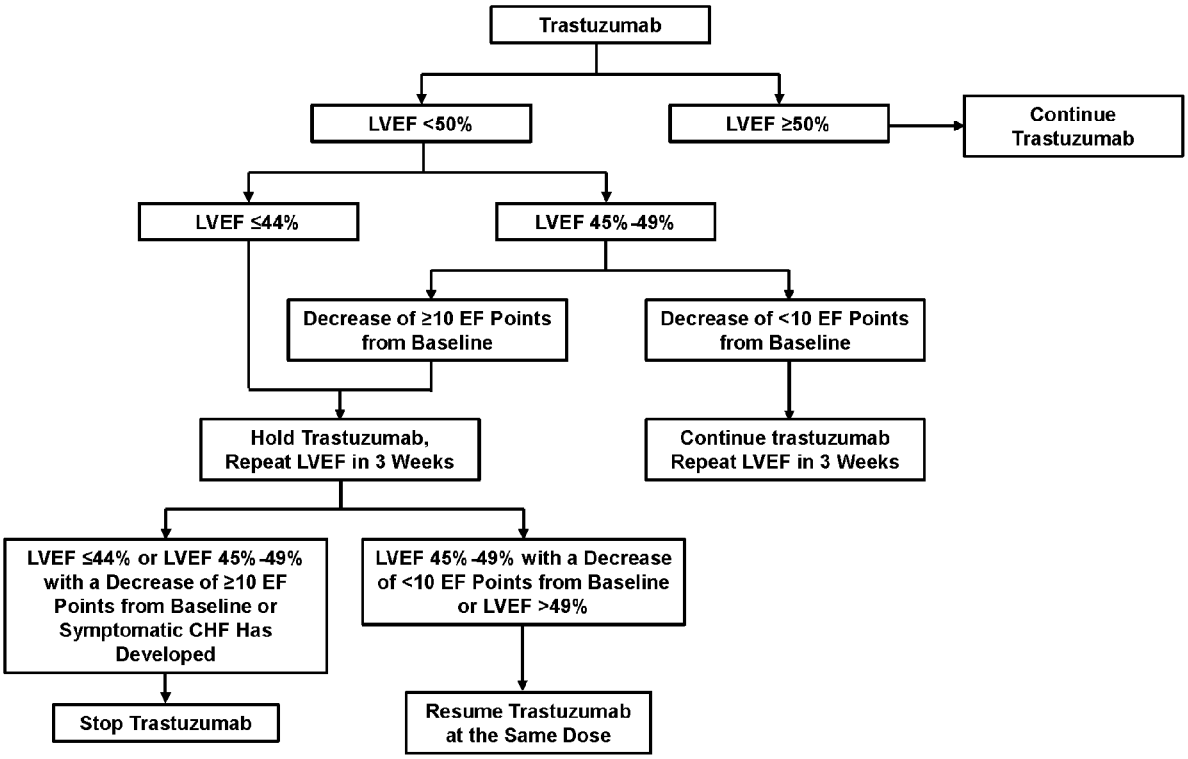
Abemaciclib must be discontinued if further dose reduction is required beyond 50 mg Q12H. In the event that abemaciclib must be discontinued, a patient may continue to receive trastuzumab and/or fulvestrant per the investigator's clinical judgment.

9.4.1.1.1.2. Trastuzumab

Dose adjustment for trastuzumab will be determined by the investigator in accordance with the label. Per the trastuzumab SPC, no reductions in the dose of trastuzumab were made during clinical trials. Patients may continue therapy during periods of reversible, chemotherapy-induced myelosuppression but they should be monitored carefully for complications of neutropenia during this time.

In the event that trastuzumab is discontinued, the patient may continue to receive abemaciclib or fulvestrant or standard-of-care single-agent chemotherapy.

For monitoring of LVEF, please refer to the algorithm in Figure JPBZ.9.1.



Abbreviations: CHF = congestive heart failure; EF = ejection fraction; LVEF = left ventricular ejection fraction.

Figure JPBZ.9.1. Algorithm for monitoring LVEF in Study JPBZ.

9.4.1.1.1.3. Fulvestrant

Dose adjustment for fulvestrant will be determined by the investigator in accordance with the label. For patients with moderate hepatic impairment (defined as Child-Pugh Class B), including any patient who develops moderate hepatic impairment during study treatment, fulvestrant 250 mg should be administered IM into the buttock slowly (1 to 2 minutes) as one 250-mg injection. In the event that fulvestrant must be discontinued, a patient may continue to receive abemaciclib and/or trastuzumab.

9.4.1.1.2. Dose Suspension (within a Cycle) and Cycle Delay

Both dose suspension (within a cycle, when applicable) and cycle delay are permitted. When a dose suspension or cycle delay occurs related to toxicity (defined as an AE possibly related to study treatment per investigator judgment), the relevant drug may be suspended or delayed as determined by the investigator's judgment and the other drug(s) may be continued.

Regardless of dose delays for other study drugs, the date of trastuzumab administration shall constitute Day 1 of the next cycle.

The start of a cycle may be delayed, or a current cycle interrupted, to allow a patient with a locoregionally recurrent breast cancer rendered operable by study treatment to receive surgery ± radiotherapy. For additional information, refer to Section 9.6.1.

9.4.1.1.2.1. Abemaciclib

Abemaciclib may be held up to 21 days to permit sufficient time for recovery from the toxicity. Patients not recovering from toxicity within 21 days should be considered for discontinuation of abemaciclib. In exceptional circumstances, a delay >21 days is permitted upon agreement between the investigator and the Lilly CRP and abemaciclib dose adjustment is to be considered.

In the event of a cycle delay due to logistical reasons (for example, due to patient availability), the patient should continue on study treatment if the patient has adequate drug supply. If a patient's treatment is interrupted as a result of not having sufficient drug supply, the cycle may be delayed up to 7 days (and not be considered a protocol violation). In exceptional circumstances, a delay >7 days is permitted upon agreement between the investigator and the Lilly CRP.

9.4.1.1.2.2. Trastuzumab

If a dose of trastuzumab is missed/omitted by 1 week or less, then the usual maintenance dose should be administered as soon as possible. Then, subsequent maintenance doses should be administered every 21 days.

If a dose is missed/omitted by more than 1 week, a re-loading dose of trastuzumab should be administered over approximately 90 minutes (8 mg/kg) as soon as possible. Subsequent trastuzumab maintenance doses (6 mg/kg) should be administered 21 days later.

If the patient requires omission of more than 2 trastuzumab maintenance doses (2 cycles) for toxicity, the patient should be withdrawn from trastuzumab.

In exceptional circumstances, a longer delay may be permitted upon agreement between the investigator and the Lilly CRP.

9.4.1.1.2.3. Fulvestrant

For fulvestrant (dosed every 4 weeks), a dose can be delayed up to 56 days from the last dose. If the patient requires more delay for toxicity, fulvestrant should be discontinued from study treatment.

In exceptional circumstances, a longer delay may be permitted upon agreement between the investigator and the Lilly CRP.

9.4.1.1.3. Management of Patients Receiving Trastuzumab and Standard-of-Care Chemotherapy

Investigators should refer to the product label (Patient Information Leaflet, Package Insert, or SPC) for trastuzumab and standard-of-care chemotherapy for guidance regarding contra-indications, duration of the contraception, dose adjustments due to toxicity, patient monitoring, and concomitant medications that are either prohibited or to be used with caution.

9.5. Blinding

This is an open-label study.

9.6. Concomitant Therapy

Appropriate documentation of all forms of premedications, supportive care, and concomitant medications must be captured at each visit in the eCRF. Concomitant medications and supportive care therapies must also be documented at the time of discontinuation and at the 30-day short-term follow-up visit.

Modulators of CYP3A

Abemaciclib is extensively metabolized through oxidation by CYP3A. In clinical drug interaction studies,

- coadministration of clarithromycin, a strong CYP3A inhibitor, increased exposure (area under the concentration time curve) to abemaciclib by 3.4-fold (Study I3Y-MC-JPBE), and
- coadministration of rifampin, a strong CYP3A inducer, decreased exposure to abemaciclib by 95% (Study I3Y-MC-JPBF).

Strong inhibitors of CYP3A (given via non-topical routes of administration) should be substituted or avoided if possible (Attachment 9). This includes grapefruit or grapefruit juice. In particular, avoid oral administration of the very strong CYP3A inhibitor, ketoconazole.

If coadministration with a strong CYP3A inhibitor is unavoidable, investigators should reduce the dose of abemaciclib by 50 mg at the start of CYP3A inhibitor treatment. That is, for patients receiving 150 mg twice daily, reduce the dose to 100 mg twice daily. For patients who have already dose reduced to 100 mg twice daily for tolerability, reduce the dose further to 50 mg twice daily. Alternatively, the investigator may consider suspending abemaciclib for the duration of the CYP3A inhibitor medication. Dose suspensions ≥28 days must be discussed with Lilly CRP/CRS.

Upon discontinuation of the strong CYP3A inhibitor, the dose of abemaciclib may be re-escalated to the dose that was used before starting the strong inhibitor after a sufficient washout period (3-5 half-lives of the strong inhibitor). Re-escalation of the abemaciclib dose requires review and approval from Lilly CRP/CRS.

Inducers of CYP3A should be substituted or avoided if possible (Attachment 9). Coadministration with a CYP3A inducer ≥28 days must be discussed with Lilly CRP/CRS.

Transporter Substrates

At clinically relevant concentrations, abemaciclib inhibits the transporters P-glycoprotein, breast cancer resistance protein, organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K. In vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin and dabigatran, may occur.

9.6.1. Surgery and/or Radiotherapy for Locoregionally Recurrent Breast Cancer

A patient with locoregionally recurrent breast cancer may receive surgery ± radiotherapy if study treatment renders the tumor operable. However, such a patient should not receive study treatment for the period beginning at least 7 days prior to surgery and continuing until at least 14 days after completion of surgery ± radiotherapy to allow for tissue healing and recovery. There is no restriction on the duration of this period without study treatment and, after this period ends, study treatment may resume. Importantly, a patient who receives surgery ± radiotherapy for locoregionally recurrent breast cancer is not considered noncompliant and does not incur a protocol deviation.

9.6.2. Palliative Radiotherapy

Palliative radiotherapy in order to palliate to symptomatic bone metastases is allowed only if limited to non-target lesions. Abemaciclib should be suspended during the palliative radiotherapy period and until complete recovery from acute reactions and potential GI toxicities, if any. Trastuzumab and or fulvestrant can be continued while on palliative radiotherapy at the discretion of the investigator.

9.6.3. Supportive Care

Patients should receive full supportive care to maximize quality of life (for example, anti-emetics, approved bone-modifying agents). Patients will receive supportive care as judged by their treating physician. If it is unclear whether a therapy should be regarded as supportive care, the investigator should consult the Lilly CRP. Use of any supportive care therapy should be reported on the eCRFs.

9.6.3.1. Supportive Management for Diarrhea

At randomization, patient should receive instructions on the management of diarrhea. In the event of diarrhea (see Attachment 10), supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, the patient should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Patients should also be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day).
- Site personnel should assess response within 24 hours.
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, abemaciclib should be suspended until diarrhea is resolved to baseline or Grade 1.
- When abemaciclib recommences dosing should be adjusted as outlined in Section 9.4.1.1.1.

In severe cases of diarrhea, the measuring of neutrophil counts and body temperature and proactive management of diarrhea with antidiarrheal agents should be considered.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibiotics such as fluoroquinolones must be prescribed.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given intravenous fluid (IV hydration) and electrolyte replacement.

9.6.3.2. Therapy for Febrile Neutropenia

Patients experiencing febrile neutropenia, especially with diarrhea or dyspnea, should be managed in a hospital setting according to standard procedures, with the urgent initiation of intravenous antibiotic therapy. Events that require a patient to be hospitalized are considered SAEs (see Section 10.3.1.1).

9.6.3.3. Growth Factors

Growth factors should not be administered to enable a patient to satisfy study inclusion criteria.

Growth factors may be administered in accordance with ASCO guidelines (Smith et al. 2015). Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be recommenced within 48 hours of the last dose of growth factors having been administered. The dose of abemaciclib must be reduced by 1 dose level on recommencement following the administration of growth factors.

9.7. Treatment Compliance

Patient compliance with study medication will be assessed at each visit.

Abemaciclib compliance will be assessed by counting returned solid oral dosage units. Study medication administration data will be recorded in the patient's medical record and eCRF.

Patients who are significantly noncompliant will be discontinued from the study. A patient will be considered significantly noncompliant if she misses 7 or more consecutive days of abemaciclib (full doses), or more than 25% cumulative days of abemaciclib (full doses) during the study. Similarly, a patient will be considered significantly noncompliant if she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Abemaciclib dose suspensions or delays related to toxicity may occur and will not result in a patient being considered as noncompliant.

Fulvestrant and trastuzumab will be administered only at the investigational sites by authorized study personnel. As a result, treatment compliance is ensured.

9.7.1. Patient Diaries

The study will include patient diaries to provide dosing instructions, help patients with treatment planning, and track actual doses of study treatment taken by the patient. Information from the diaries may be used for documenting study treatment compliance as well as dosing time relative

to PK blood draws and electrocardiogram (ECG) collection. For patients randomized to either abemaciclib arm (Arm A or Arm B), diaries for Cycles 1 through 4 are mandatory. Diaries beyond Cycle 4 are optional.

10. Efficacy, Health Outcome/Quality of Life Measures, Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Written informed consent must be obtained prior to any study-specific pretreatment evaluations.

Study procedures related to efficacy, safety, health outcome/quality of life measures, sample collection and testing assessments and their timing are described in the sections below and shown in the Study Schedule (Attachment 1).

10.1. Efficacy Measures

10.1.1. Efficacy Assessments at Baseline and During Study Treatment

Within 28 days of randomization, baseline tumor assessments will be performed for each patient. The method of assessment used at baseline must be used consistently for serial tumor assessment throughout the study. Bone scintigraphy (bone scan) will be performed for ALL patients at baseline (within 28 days of randomization). However, prior bone scintigraphy (obtained as part of routine clinical care) within 45 days before randomization is also acceptable. For patients with treated brain metastases, a gadolinium-enhanced magnetic resonance imaging scan will be performed at baseline. Note: progressive brain metastases will be considered PD, and patients will be discontinued from the study (Section 7.3.2). All tumor assessment images must be submitted for potential central review.

ONLY for patients **with bone lesions** identified on baseline bone scintigraphy, repeat bone scintigraphy every 24 weeks (that is, every 6 months [± 3 business days]) in order to detect new lesions. Additional bone scintigraphy should be considered if there is clinical suspicion of disease progression in bone. If a patient with bone lesions at baseline experiences a CR, bone scintigraphy should continue to be repeated every 24 weeks (± 3 business days) and until disease progression to detect new lesions.

- Note: For patients **with no bone lesions** on baseline bone scintigraphy, bone scintigraphy should be performed ONLY if there is clinical suspicion of disease progression in bone, even if a CR is achieved.

For bone lesion measurements, if chest/abdomen/pelvis CT (CAP CT)/MRI does not capture bone lesions, perform specific bone-directed imaging (X-ray, CT scan with bone windows, or MRI) at baseline and repeatedly every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression. **EXCEPTION:** For the following patients, **NO** specific bone-directed imaging is required:

- patients with **no** bone lesions at baseline
- patients with measurable visceral disease and nonmeasurable bone lesions

The same imaging method used at baseline for bone lesion measurement is to be used during treatment period and follow-up.

For all patients, imaging studies (CT, including spiral CT, or MRI scan of the chest, abdomen, and pelvis) will be performed locally at baseline and will be repeated every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression per the Study Schedule (Attachment 1). It is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast, whenever possible. For patients with known hypersensitivity to CT contrast material, a CT scan of the chest without contrast and gadolinium-enhanced MRI of the abdomen and pelvis are encouraged. The CT portion of a positron emission tomography (PET)-CT scan may be used as a method of response assessment if the site can document that the CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). A PET scan alone or as part of a PET-CT may be performed as part of routine clinical care but cannot be used to assess response according to RECIST v1.1.

For patients with ONLY locally advanced disease extension and NO measurable lesions out of the breast on CAP CT scan, MRI scan of the breast will be performed at baseline. Breast MRI, if applicable, will be repeated every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression.

For patients with visible tumors (such as skin lesions), photography will be performed at baseline and every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression. Each photographic image of the tumor should include a ruler. Photographic images may be taken more frequently based upon the discretion of the investigator or following the identification of new skin lesions post-baseline.

For patients continuing treatment during the Continued Access Period (after study completion), efficacy assessments (frequency and type of assessments) will be at the discretion of the investigator.

10.1.2. Efficacy Assessments during Postdiscontinuation Follow-Up

Postdiscontinuation follow-up during the study period will be conducted as described in the Study Schedule (Attachment 1).

For those patients who are randomized and never receive study treatment or those who discontinue study treatment without objectively measured PD, the investigative sites will continue to monitor patients and periodically evaluate tumor response via measurement of visible tumors and radiological imaging approximately every 6 weeks for 36 weeks from first dose of study therapy and thereafter approximately every 9 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression, or until primary analysis of PFS. Bone scintigraphy, only for patients with bone lesions on baseline scintigraphy, is to be performed approximately every 24 weeks until objective disease progression or primary

PFS analysis. In addition, anticancer therapies initiated after study treatment discontinuation will be collected during this follow-up period. After the patient has objective disease progression, radiologic tests and photographic images are no longer required and the patient will continue with postdiscontinuation follow-up approximately every 9 weeks until the patient's death or overall study completion.

Lilly will continue to collect survival data on all patients but may reduce data collection for other efficacy data. Lilly will notify investigators when this reduced data collection can begin.

10.1.3. Primary Efficacy Measure

The primary efficacy measure is investigator-assessed PFS as defined by RECIST 1.1 (Eisenhauer et al. 2009) provided in Attachment 5.

Lilly or its designee will collect and store all tumor measurement images on all enrolled patients throughout the study. Digital images are to be sent to a third-party organization (TPO) for storage.

The PFS time is measured from the date of randomization to the date of objective progression or the date of death due to any cause, whichever is earlier. The censoring is taken in the following order:

- if a patient does not have a complete baseline disease assessment, then the PFS time will be censored at the enrollment date, regardless of whether or not objectively determined disease progression or death has been observed for the patient; otherwise,
- if a patient is not known to have died or have objective progression as of the data inclusion cutoff date for the analysis, the PFS time will be censored at the last complete objective progression-free disease assessment date.

Detailed censoring rules are described in Table JPBZ.12.1.

The study will admit patients with both measurable and/or nonmeasurable disease. For those patients with nonmeasurable, bone-only disease, objective progression will be established if at least 1 of the following criteria is met based on RECIST v1.1:

- the appearance of 1 or more new lesions (in bone or outside of bone), or
- unequivocal progression of existing bone lesions

According to RECIST v1.1, the finding of a new lesion should be unequivocal and not attributable to findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of preexisting lesions). Pathologic fracture, new compression fracture, or complications of bone metastases will not be considered as evidence of disease progression, unless at least 1 of the above criteria is met.

For those patients with locally-advanced recurrent breast cancer for whom surgery is performed with no evidence of residual disease post-operatively, objective progression will be established if at least 1 of the following criteria is met:

- local and/or regional recurrence, or

- new development of metastatic disease.

For those patients with locally-advanced recurrent breast cancer for whom surgery is performed while on study with evidence of residual disease post-operatively, new baseline measurements should be taken and RECIST applied. After surgery, restart tumor assessment according to the Study Schedule (Attachment 1) (that is, every 6 weeks for 36 weeks, then every 9 weeks).

10.1.4. Secondary Efficacy Measures

The following secondary efficacy measures (Table JPBZ.10.1) will be collected at the times shown in the Study Schedule (Attachment 1).

Table JPBZ.10.1. Secondary Efficacy Endpoints

Endpoint	Definition
Overall Survival	The time from the date of study enrollment to the date of death from any cause
Objective Response Rate	The proportion of patients with CR or PR according to RECIST v1.1
Duration of Response (DoR)	The time from the date of first evidence of CR or PR to the date of objective progression (according to RECIST v1.1) or death from any cause, whichever is earlier
Disease-Control Rate (DCR)	The proportion of patients with CR, PR, or SD according to RECIST v1.1
Clinical Benefit Rate (CBR)	The proportion of patients with CR, PR, or SD ≥6 months according to RECIST v1.1

Abbreviations: CR = complete response; PR = partial response; PS = performance status; RECIST = Response Evaluation Criteria In Solid Tumors; SD = stable disease.

Overall Survival (OS): Overall survival duration is measured from the date of randomization of any study drug to the date of death from any cause. For each patient who is not known to have died as of the data-inclusion cutoff date for a particular analysis, OS will be censored for that analysis at the last known alive date.

Objective Response Rate (ORR): The objective response rate is the percentage of patients with a best response of CR or PR.

Duration of Response (DoR): The DoR is defined only for responders (patients with a CR or PR). It is measured from the date of first evidence of a CR or PR to the date of objective progression or the date of death due to any cause, whichever is earlier. If a responder is not known to have died or have objective progression as of the data inclusion cutoff date, DOR will be censored at the date of the last complete objective progression-free disease assessment.

Disease Control Rate (DCR): The DCR is the percentage of patients with a best response of CR, PR, or SD.

Clinical Benefit Rate (CBR): The CBR is the percentage of patients with a best response of CR or PR, or SD for at least 6 months.

10.2. Health Outcome/Quality of Life Measures

10.2.1. Patient-Reported Outcomes

The primary health outcomes research goal is to determine if abemaciclib combination therapy is able to palliate pain, as measured by the mBPI-sf (Cleeland 1991). Additionally, the EORTC QLQ-C30 (Aaronson et al. 1993) will assess the broader impact of abemaciclib combination therapy on quality of life, and the EQ-5D 5L (Janssen et al. 2008) health status assessment will allow for comparison with other tumor types and disease states.

Patient-reported questionnaires should be completed by patients when a language translation is available in which the patient is fluent or literate.

At each time point identified in the Study Schedule (Attachment 1), a paper copy of the mBPI-sf, EORTC QLQ-C30, and EQ-5D 5L questionnaires should be administered to the patient prior to extensive interaction with site staff and study drug administration.

10.2.1.1. Pain Intensity

The mBPI-sf (Cleeland 1991) is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for patients to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, and enjoyment of life).

Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (*no pain* or *does not interfere*) and ranged through 10 (*pain as bad as you can imagine* or *completely interferes*). The mBPI-sf recall period is 24 hours, and pain relief is assessed with a scale range from 0% (*no relief*) through 100% (*complete relief*). Typical completion time for this instrument is less than 5 minutes. Focused analysis will be on "worst pain".

Use of pain medication will be assessed in conjunction with the mBPI-sf assessment. Data on each individual prescription and over-the-counter analgesic medication will be recorded on the Concomitant Medications eCRF. The use of pain medications should be reviewed with the patient at each subsequent visit. Any changes to analgesic use (new or stopped analgesics) will be recorded on the eCRF. Pain medication will be classified into 1 of 3 categories, using an analgesic ladder approach with medication category based on a World Health Organization (WHO) pain relief ladder: nonopioids (aspirin and paracetamol); then, as necessary, mild opioids (codeine); then strong opioids such as morphine (WHO cancer pain ladder page [WWW]). A therapy category will be assigned according to the maximum category of therapy administered based on analgesic data for that cycle. Category of pain medication for each cycle will be determined based on the data collected on analgesic use.

The BPI population will include all patients who completed at least 1 baseline followed by at least 1 BPI "worst pain" assessment after 1 cycle of study drug (Cycle 2 Day 1 or later).

10.2.1.2. Health-Related Quality of Life

Broadly used in cancer trials, validated, and available in over 80 different languages, the EORTC QLQ-C30 (Aaronson et al. 1993) is a reliable and validated tool. The EORTC QLQ-C30 self-reported general cancer instrument (Aaronson et al. 1993) consists of 30 items covered by 1 of 3 dimensions:

- global health status/quality of life (2 items)
- functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning)
- symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)

The EORTC QLQ-C30 questionnaire is administered per the Study Schedule (Attachment 1). The recall period is the past week, completion time is typically 5 to 7 minutes, and the questionnaire will be scored as described by the EORTC scoring manual (Fayers et al. 2001). The EORTC population will include all patients who completed at least 1 baseline followed by at least 1 EORTC assessment after 1 dose of study drug (Cycle 2 Day 1 or later).

10.2.1.3. Health Status

The EQ-5D 5L (Janssen et al. 2008) is a standardized instrument for use across diseases as a measure of self-reported health status. Specifically, this questionnaire is included in this trial to evaluate health-state utilities associated with advanced breast cancer. These utility measures are an important input for economic evaluations concerning the value of treatment interventions.

The EQ-5D 5L is designed to be used in conjunction with other patient-reported measures. Patients will complete the 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), 5-level (no problem, slight, moderate, severe, or extreme problem) assessment according to the Study Schedule (Attachment 1). A visual analog scale (VAS) "thermometer" measures current health state.

Administration is preferably scheduled after the BPI and the EORTC, and before extensive contact with study personnel or clinicians, which could result in biased patient response. The recall period is “today.” The EQ-5D 5L is designed for self-completion by respondents and is cognitively simple, taking only a few minutes to complete.

The EQ-5D 5L population will include all patients who completed at least 1 baseline followed by at least 1 EQ-5D 5L assessment after 1 dose of study drug.

10.2.2. Resource Utilization

Investigators will be asked to document the use of all concomitant medications, transfusions, and treatment-related hospitalization days. Such assessments are to be taken throughout the study up to the 30-day short-term postdiscontinuation follow-up visit.

10.3. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious, considered related to the study, or that caused the patient to discontinue before completing the study. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

The timing of all safety evaluations is shown in the Study Schedule (Attachment 1). Table JPBZ.10.2 presents a summary of AE and SAE reporting guidelines. Table JPBZ.10.2 also shows which database or system is used to store AE and SAE data.

Table JPBZ.10.2. Adverse Event and Serious Adverse Event Reporting Guidelines

Period	Types of AEs/SAEs to be Reported	Collection Database	Lilly Safety System
Baseline (pretreatment)	Preexisting conditions	x	
	All AEs	x	
	SAEs related to protocol procedures	x	x
Study treatment period	All AEs	x	
	All SAEs	x	x
30-day short-term postdiscontinuation follow-up	All AEs	x	
	All SAEs	x	x
Long-term postdiscontinuation follow-up	All SAEs related to protocol procedures or study drugs	x	x
Continued access period	All AEs	x	
	All SAEs	x	x
Continued access follow-up	All AEs	x	
	All SAEs	x	x
After the patient is no longer participating in the study (that is, no longer receiving study treatment and no longer in follow-up)	All SAEs related to protocol procedures or study drug that the investigator becomes aware of		x

Abbreviations: AEs = adverse events; SAEs = serious adverse events.

10.3.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical study AE is any untoward medical event associated with the use of a drug in humans, whether or not it is considered related to that drug.

Lack of drug effect is not an AE in clinical trials, because the purpose of the clinical trial is to establish drug effect.

Any clinically significant findings from ECGs, labs, vital sign measurements, and other procedures that result in a diagnosis should be reported to Lilly or its designee.

Cases of pregnancy that occur during maternal exposures to study treatment should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation

Study site personnel will record the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

After the ICF is signed, site personnel will record the occurrence and nature of any AEs and any change in the preexisting condition(s). All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of study treatment must be reported to Lilly or its designee via eCRF.

Investigators will be instructed to report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure and study treatment via eCRF.

The investigator will decide whether he or she interprets the observed AEs as related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to study treatment or study procedure, the following terminologies are defined:

- **Probably related**: a direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Does not know:** the investigator cannot determine
- **Not related**: without question, the AE is definitely not associated with the study treatment

The investigator should classify all "probably related," "possibly related," or "does not know" AEs and SAEs as related to study treatment/study procedure.

Patients will be evaluated for AEs at each visit and will be instructed to call their physician to report any AEs between visits.

The National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) v 4.03 will serve as the reference document for choosing appropriate terminology for, and grading the severity of, all AEs and other symptoms. For AEs without matching terminology within the NCI-CTCAE v 4.03 criteria, the investigator will be responsible for selecting the appropriate system organ class and assessing severity grade based on the intensity of the event.

In addition to collecting the AE verbatim and the CTCAE severity grade, AE verbatim text will also be mapped by Lilly or its designee to corresponding terminology within the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

If a patient's dosage is reduced or treatment is discontinued as a result of an AE, study site personnel must clearly report to Lilly or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

10.3.1.1. Serious Adverse Events

An SAE is any adverse event from this study that results in one of the following outcomes:

- death
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- initial or prolonged inpatient hospitalization
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious adverse event collection begins after the patient has signed informed consent and has received study treatment. If a patient experiences an SAE after signing informed consent, but prior to receiving study treatment, the event will not be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly Safety System.

Study site personnel must alert Lilly or its designee of any **serious** adverse event (SAE) within 24 hours of investigator awareness of the event via a sponsor-approved method. If study site personnel contact Lilly or its designee by telephone regarding an SAE, study site personnel must also immediately provide official notification on study-specific SAE forms.

This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Planned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study treatment or other protocol-required procedure) should not be considered SAEs.

Serious adverse events due to disease progression, including death, should not be reported unless the investigator deems them to be possibly related to the study treatment.

If an investigator becomes aware of an SAE occurring after the patient's participation in the trial has ended, and the investigator believes that the SAE is related to a protocol procedure or study treatment, the investigator should report the SAE to the sponsor, and the SAE will be entered in the Lilly Safety System.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by the sponsor in aggregate periodically during the course of the trial may be found in the IB.

10.3.1.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Reference Safety Information (RSI) in the IB and that the investigator identifies as related to the study treatment or study procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and associated detailed guidances.

10.3.2. Other Safety Measures

10.3.2.1. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1). Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline, is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation.

10.3.2.2. Assessment of LVEF by Echocardiography or Multigated Acquisition Scan

Since trastuzumab will be administered to all patients, an echocardiography or MUGA scan is required at baseline within 45 days of randomization. Only subjects with LVEF of 50% or higher should be enrolled in the study. During study treatment period, echocardiography or MUGA scan is performed at Cycle 5 Day 1 (±7 days). Then, if LVEF is stable, echocardiography or MUGA is repeated every 12 weeks starting with Cycle 9 Day 1 (± 7 days) and then every 24 weeks following discontinuation of trastuzumab. If LVEF on trastuzumab therapy is <50%, refer to LVEF monitoring diagram in Figure JPBZ.9.1.

In addition, during the course of trastuzumab therapy, subjects should be monitored for signs and symptoms of congestive heart failure (dyspnea, tachycardia, new unexplained cough, neck vein distention, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and rapid unexplained weight gain). Any subject who develops clinical signs or symptoms of congestive heart failure should undergo an ECG and assessment of LVEF by either echocardiogram or MUGA scan.

10.3.3. Safety Monitoring

The Lilly CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and review:

- trends in safety data
- laboratory analytes
- AEs

10.3.3.1. Special Hepatic Safety Data Collection

Liver testing (Attachment 3), including ALT, AST, alkaline phosphatase, total bilirubin (TBL), direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase, should be repeated within 2 to 4 days to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of…	develops the following elevations:
ALT or AST <1.5× ULN	ALT or AST ≥5× ULN or ALT or AST ≥3× ULN concurrent with TBL ≥2× ULN
ALT or AST ≥1.5×ULN	ALT or AST ≥3× baseline or ALT or AST ≥2× baseline concurrent with TBL ≥2× ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal.

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical

examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), history of concomitant medications (including over-the-counter, herbal and dietary supplements, history of alcohol drinking, and other substance abuse). In addition, the evaluation should include a blood test for prothrombin time international normalized ratio (PT-INR); serological tests for viral hepatitis A, B, C, E, autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Additional Hepatic Safety Collection

Additional safety data should be collected via the case report form (CRF) if 1 or more of the following conditions occur:

In participants enrolled with baseline ALT or AST <1.5× ULN

- Elevation of serum ALT or AST to ≥5× ULN on 2 or more consecutive blood tests
- The combination of elevated ALT or AST ≥3× ULN and elevated TBL ≥2× ULN

In participants enrolled with baseline ALT or AST ≥1.5× ULN

- Elevated ALT or AST ≥3× baseline on 2 or more consecutive tests
- The combination of elevated ALT or AST ≥2× baseline and elevated TBL ≥2× ULN

In all study participants

- Discontinuation from study treatment due to a hepatic event or abnormality of liver tests
- Occurrence of a hepatic event considered to be an SAE

10.3.3.2. Renal Function

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion of creatinine without affecting cystatin C-calculated glomerular filtration rate. Increases in serum creatinine occurred within the first 2 weeks of treatment, remained stable through the treatment period, and were reversible upon treatment discontinuation. If deterioration of renal function is suspected, serum creatinine should not be the only measure used to assess a patient's renal function.

Dose adjustment (omission, reduction, or discontinuation) should not solely be based on interpretation of serum creatinine values because these may not reflect renal function. If deterioration of renal function is suspected per the investigator's clinical assessment, dose alteration should follow the protocol guidance for non-hematological toxicities (Table JPBZ.9.2).

A serum cystatin C will be collected with the central chemistry laboratory sample.

10.3.3.3. Venous Thromboembolic Events

VTE has been identified as an adverse drug reaction for abemaciclib in combination with endocrine therapy. In the randomized Phase 3 studies in patients with breast cancer treated with abemaciclib in combination with endocrine therapy (ET), a greater number of patients

experienced VTEs in the abemaciclib plus ET arm than in the placebo plus ET arm or ET alone arm. The majority of patients who experienced VTEs were treated with anticoagulants. At this time, the mechanism underlying the association between abemaciclib and the occurrence of VTEs is not known. Monitor patients for signs and symptoms of deep vein thrombosis and pulmonary embolism and treat as medically appropriate.

10.3.3.4. Interstitial Lung Disease/Pneumonitis

Interstitial lung disease/pneumonitis has been identified as an adverse drug reaction for abemaciclib. The majority of events observed in clinical trials were Grade 1 or Grade 2, with serious cases and fatal events reported. Additional information is available in the IB.

Ask your patients to report any new or worsening pulmonary symptoms, such as dyspnea, cough, and fever, and investigate and treat as per your local clinical practice (including corticosteroids as appropriate). If ILD/pneumonitis is suspected, investigations may include imaging, such as high-resolution computed tomography, bronchoalveolar lavage, and biopsy as clinically indicated.

Refer to Table JPBZ.9.2 for guidance on dose adjustments of abemaciclib for patients with ILD/pneumonitis (see Attachment 10 for ILD/pneumonitis CTCAE grades). Discontinue abemaciclib in cases of severe (Grade 3 or 4) ILD/pneumonitis.

10.3.4. Complaint Handling

Lilly collects product complaints on study treatment used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to comparator drugs or concomitant drugs are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated AEs using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to Lilly or its designee

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.4. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the specific tests that will be performed for this study and whether these will be performed at a central or local laboratory.

Attachment 6 lists the schedule for PK sampling during the study.

Attachment 7 provides a summary of the estimated maximum number and volume of invasive samples, for all sampling, during the study.

10.4.1. Samples for Study Qualification and Health Monitoring

Blood samples will be collected to determine whether patients meet inclusion/exclusion criteria and to monitor patient health. Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory results that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.

Investigators must document their review of each laboratory safety report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Tests are run and confirmed promptly whenever scientifically appropriate. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.4.2. Samples for Pharmacogenetics and Biomarkers

There is growing evidence that genetic variation may impact a patient's response to therapy. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, where local regulations and ERBs allow, a blood sample will be collected for pharmacogenetic analysis.

Biomarker research is used to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety) and clinical outcome. Specimen storage is incorporated in clinical trials to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, other cellular elements.

As part of Lilly's ongoing efforts to understand the relationship between cancer, genetics, and response to therapy, this study will analyze biomarkers relevant to abemaciclib, trastuzumab, fulvestrant, the cell cycle, and/or breast cancer. The study will analyze the correlation between biomarkers and clinical outcome and may be used for related research methods or validation of diagnostic tools or assays.

Samples for biomarker research will be collected at times specified in Attachment 1.

Required samples for biomarker research to be collected from all patients in this study are the following:

- Whole blood sample for genetic research (pharmacogenetic analysis)
- Plasma for biomarkers
- Tumor tissue (newly obtained; otherwise archived)

10.4.2.1. Whole Blood Sample for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in Study Schedule (Attachment 1).

In the event of an unexpected AE or the observation of unusual response, the pharmacogenetic biomarker samples may be genotyped and analysis may be performed to evaluate a genetic association with response to study treatment. These investigations may be limited to a focused candidate gene study or, if appropriate, genome wide analysis may be performed to identify regions of the genome associated with the variability observed in drug response. The pharmacogenetic biomarker samples will only be used for investigations related to disease and drug or class of drugs under study in the context of this clinical program. They will not be used for broad exploratory unspecified disease or population genetic analysis.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment.

Molecular technologies are expected to improve during the 15 year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, candidate gene studies, and epigenetic analyses. Regardless of the technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

10.4.2.2. Biomarkers

10.4.2.2.1. Plasma

Plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Study Schedule (Attachment 1) where local regulations allow.

Samples will be used for research on the cell cycle, breast cancer, mechanism of action associated with study treatment, and/or research method or in validating diagnostic tools or assay(s) related to breast cancer.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment.

10.4.2.2.2. Tumor Tissue

The availability of adequate tumor tissues is important to better characterize the relationship of tumor biology and response evaluation in this study. As such, this study is requesting submission of tumor tissue (newly biopsied; otherwise archived) to support correlative studies.

Availability of either newly obtained biopsy **OR** archived tumor sample is mandatory at baseline; collection of fresh biopsy at baseline is preferred. If collection of fresh biopsy is not possible, submission of archived tumor specimen is mandatory, unless restricted by local

regulations. Sites should confirm the availability of adequate tumor tissue with the pathological laboratory prior to randomization. Additionally, a biopsy will be requested during Postdiscontinuation Follow-Up from patients who discontinue due to PD; this postdiscontinuation biopsy is contingent upon patient consent, and the tumor tissue will potentially be used to explore mechanisms of resistance to abemaciclib.

Formalin-fixed paraffin-embedded tumor tissue should be provided as a block or unstained slides. Sites should submit a minimum of 20 slides. Due diligence should be used to make sure that tumor specimen (not a normal adjacent or a tumor margin sample) is provided. Pathology notes accompanying archival tissue may also be requested. The report must be coded with the patient number. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission. Blocks will be sectioned and returned to the site. Slides will not be returned.

Tumor tissue will be examined for biomarkers that may include, but are not limited to, those related to breast cancer, study treatment and/or cell cycle.

In addition, centralized HER2 receptor testing will be conducted post-randomization and in an exploratory manner for all patients on the tumor tissue collected at baseline. Testing will be performed according to ASCO/CAP HER2 guidelines (Wolff et al. 2013).

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ERBs impose shorter time limits, at a facility selected by the sponsor. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in drug development or when the drug is commercially available.

The samples will be coded with the patient number and stored for up to a maximum 15 years after the last patient visit for the study at a facility selected by the sponsor. The samples and any data generated from them can only be linked back to the patient by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study treatment.

Technologies are expected to improve during the 15 year storage period and therefore cannot be specifically named. However, existing approaches including mutation profiling, copy number variability, gene expression, and/or immunohistochemistry may be performed on these tissue samples to assess potential associations with these biomarkers and clinical outcomes.

10.4.3. Samples for Drug Concentration Measurements Pharmacokinetics

Pharmacokinetic samples will be collected as specified in the Pharmacokinetic Sampling Schedule (Attachment 6).

Blood samples will be used to determine the concentrations of abemaciclib and its metabolites, as well as trastuzumab and fulvestrant in patients enrolled on Arms A and B.

Bioanalytical samples collected to measure abemaciclib, fulvestrant, and trastuzumab concentrations will be retained for a maximum of 1 year following last patient visit for the study.

10.5. Appropriateness of Measurements

Efficacy measurements by radiographic imaging are standard, widely used, generally recognized as reliable, accurate, and able to discriminate between effective and ineffective agents.

Safety measurements by laboratory monitoring are standard, widely used, generally recognized as reliable, accurate, and able to discriminate between agents with acceptable and unacceptable safety profiles.

11. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- sponsor start-up training to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this trial. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly laboratory database.

Any data for which the paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, a rating scale), a daily dosing schedule, or an event diary.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

The primary objective of this study is to compare abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab in terms of PFS in patients with locally advanced recurrent or metastatic breast cancer. The study will enroll approximately 225 patients in [1:1:1] randomization (75 patients in abemaciclib plus trastuzumab plus fulvestrant; 75 patients in abemaciclib plus trastuzumab; and 75 patients in standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab). The primary analysis will be performed after approximately 165 PFS events have occurred. Assuming a hazard ratio of 0.667, this sample size yields at least 80% statistical power to detect superiority of the abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab arms over standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab arm with the use of an experiment-wise 1-sided alpha level of .10.

If the true median PFS for the standard-of-care single-agent chemotherapy of physician's choice plus trastuzumab arm is 4 months, then the HR of 0.667 amounts to an approximately 2-month improvement in median PFS for the abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab arms under an additional assumption of exponential survival distribution. Assuming a censoring rate of approximately 30%, the study will randomize approximately 225 patients.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly.

Efficacy analyses will be based on the intention-to-treat (ITT) analysis set. This population is defined as all patients randomized to study treatment. Patients will be grouped according to randomized treatment.

Safety analyses will be based on the Safety Population, defined as all enrolled patients receiving at least 1 dose of any study drug. Patients will be grouped according to treatment received in cycle 1.

Pharmacodynamic and/or tailoring biomarker analyses will be based on the subset of patients from the above populations from whom a valid assay result (according to laboratory guideline) has been obtained.

All tests of treatment effects will be conducted at a 2-sided alpha, unless otherwise stated. All confidence intervals (CIs) will be given at a 2-sided 95% level, unless otherwise stated. For regulatory purposes, tests may be performed at a 1-sided alpha level of 0.025, with 95% CIs.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol.

Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

The assumptions for each statistical method will be evaluated. If there is violation of assumptions, alternative statistical methods may be used.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

12.2.2. Patient Disposition

A detailed description of patient disposition will be provided. It will include a summary of the number and percentage of patients entered into the study, enrolled in the study, and treated as well as number and percentage of patients completing the study, or discontinuing (overall and by reason for discontinuation). A summary of all important protocol deviations will be provided.

12.2.3. Patient Characteristics

Patient characteristics will include a summary, by treatment arm, of the following:

- patient demographics
- baseline disease characteristics
- preexisting conditions
- historical illnesses
- prior endocrine therapy
- prior chemotherapy (including both cytotoxic and targeted agents)
- prior HER2-directed therapy

Other patient characteristics will be summarized as deemed appropriate.

12.2.4. Concomitant Therapy

Concomitant medications will be summarized for the safety population.

12.2.4.1. Postdiscontinuation Therapy

The numbers and percentages of patients reporting postdiscontinuation therapies will be provided overall, by type of therapy (surgery, radiotherapy, or chemotherapy), and by drug name.

12.2.5. Treatment Compliance

The number of dose omissions, reductions, delays, the number of cycles received, and dose intensity will be summarized for all treated patients per treatment arm.

Treatment compliance information for abemaciclib will be collected through pill counts at each visit and the number of tablets taken relative to the number expected to be taken will be summarized.

12.2.6. Primary Outcome and Methodology

The primary endpoint of this study is PFS. Progression-free survival time is measured from the date of randomization to the date of investigator-determined objective progression as defined by

RECIST v1.1, or death from any cause. Patients who have neither progressed nor died will be censored at the day of their last radiographic tumor assessment (if available) or date of randomization if no post initiation (that is, post-baseline) radiographic assessment is available. The detailed censoring rules are described in Table JPBZ.12.1.

Table JPBZ.12.1. Rules for Determining Date of Progression or Censor for Progression-Free Survival

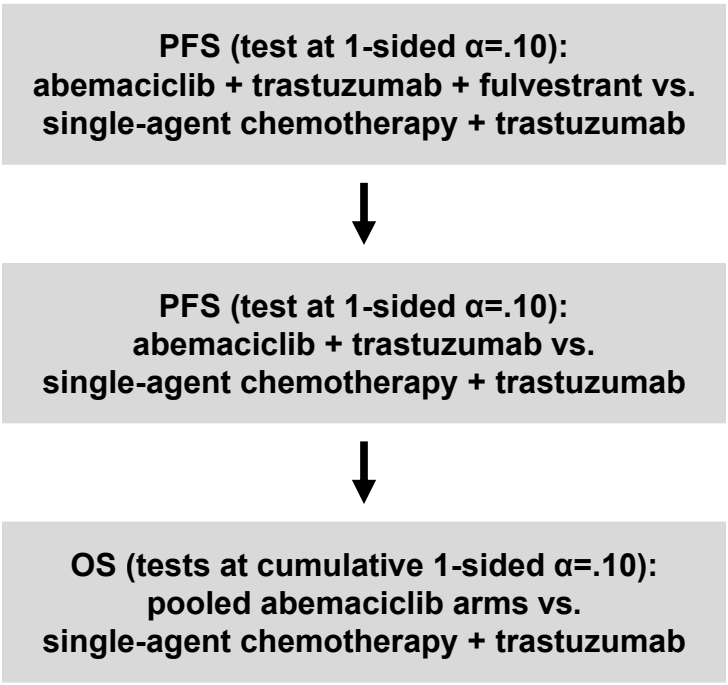
Situation	Date of Event or Censor	Event / Censor
Tumor progression or death	Earliest date of PD or death	Event
No tumor progression and no death	Date of last adequate radiological assessment or date of randomization (whichever is later)	Censored
Unless		
No baseline radiological tumor assessment available	Date of randomization	Censored
No adequate post baseline radiological tumor assessment available and death reported after 2 scan intervals following randomization	Date of randomization	Censored
New anticancer treatment started (excluding maintenance endocrine therapy following chemotherapy) and no tumor progression or death within 14 days	Date of adequate radiological assessment prior to (start of new therapy +14 days) or date of randomization (whichever is later)	Censored
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)	Date of last adequate radiological assessment or date of randomization (whichever is later)	Censored

Abbreviations: PD = progressive disease.

The PFS analysis to test the superiority of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to chemotherapy plus trastuzumab in improving PFS time will be performed on the ITT population and will use the log-rank test stratified by number of previous regimens for advanced breast cancer and status of disease. In addition, the Kaplan-Meier method (Kaplan and Meier 1958) will be used to estimate the PFS curves as well as PFS rates at every 3 months for each treatment group. These rates will be compared based on a normal approximation for the difference between the rates.

There is 1 planned primary analysis for PFS in this study, which will be performed after approximately 165 events have been observed in the ITT population based on investigator assessment. The primary PFS analysis will compare each arm against the control using a log rank test stratified by the randomization factors. The primary objective of PFS will be tested at an experiment-wise 1-sided alpha level of .10. The abemaciclib treatment arms will be tested sequentially against the trastuzumab plus chemotherapy arm, with the abemaciclib plus trastuzumab plus fulvestrant arm tested first. A comparison of the 2 abemaciclib arms will be considered exploratory. See Figure JPBZ.12.1 for a depiction of alpha spending. A stratified

Cox proportional hazard model (Cox 1972) with treatment as a factor will be used to estimate the HR and corresponding CI with Wald's test p-value after adjusting for the same randomization variable specified for the primary analysis. An additional unstratified Cox regression model will be employed to explore the effects of prognostic variables, such as of the stratification variables and intrinsic/extrinsic factors, on treatment response.



Abbreviations: OS = overall survival; PFS = progression-free survival; vs. = versus.

Figure JPBZ.12.1. Alpha spending for Study I3Y-MC-JPBZ.

12.2.7. Other Analyses of Efficacy

12.2.7.1. Overall Survival

Overall survival is an important secondary endpoint for this study. Overall survival will be tested only if PFS is significant for both abemaciclib arms. Overall survival will be tested by pooling the 2 abemaciclib arms and comparing them against the chemotherapy arm. Up to a total of 2 interim analyses and a final analysis for OS may be performed in this study. The type I experiment-wise error rate will be controlled at 10% by using the Lan-Demets method with the following O'Brien-Fleming like α-spending function:

$$\alpha^*(t_k) = 2\left(1 - \Phi\left(\Phi^{-1}(1-\alpha/2) \Big/ \sqrt{t_k}\right)\right).$$

Here, t_k is the information fraction at time k, Φ is the standard normal cumulative distribution function, and Φ^{-1} is the standard normal quantile function.

The actual alpha spent will be calculated based on the actual number of events observed at the time of analysis using software that implements the alpha-spending function noted above (for example, ADDPLAN 6.0 or SAS 9.2).

To maintain the experiment-wise type I error rate, OS will be hierarchically tested in the following way: only if the test of PFS is significant will OS also be tested inferentially for significance (Glimm et al. 2010); specifically:

- The first potential time point for OS analysis will be at the time of the PFS analysis. If PFS is significant at this stage, the first interim analysis of OS will also be performed. If OS is not significant at this stage, the second interim analysis of OS will be performed after approximately 105 deaths have been observed in the ITT population (information fraction of 0.667). If OS is not significant at this stage, a final analysis will be performed after approximately 158 deaths have been recorded in the ITT population.
- If the primary analysis for PFS is not significant, OS will not be statistically evaluated.

The OS analysis to test the superiority of abemaciclib plus trastuzumab plus fulvestrant and abemaciclib plus trastuzumab to chemotherapy plus trastuzumab in improving OS time will use the log-rank test stratified by the number of previous systemic regimens for advanced breast cancer and disease status.

The following additional analyses will be conducted for OS:

- Kaplan-Meier curves (Kaplan and Meier 1958) will be generated; medians, quartiles, and appropriate point probabilities with interval estimates will be calculated.
- The Cox regression stratified by the randomization factors will be used to estimate the HR between the 2 treatment groups, along with CI.

In addition, OS rate at 1 year in each treatment arm will be calculated by determining OS time for each patient and using Kaplan-Meier techniques to assess OS time for each treatment arm. The Kaplan-Meier estimate of the OS rate at 1 year will be used to compare treatment arms using a standard normal test of the difference in OS rate at 1 year. The same techniques will be used to calculate and compare OS rates at 2 years and 3 years between arms.

12.2.7.2. Other Analyses of Secondary Efficacy Endpoints

Other secondary efficacy endpoints will be defined as shown in Table JPBZ.10.1. Objective response rate, DCR, and CBR of each treatment arm will be calculated using the ITT population. All rates will be compared between the 3 treatment arms based on a normal approximation for the difference between the rates. Duration of response time is defined only for responders (patients with a best response of CR or PR). A Kaplan-Meier analysis of DoR will be performed to estimate the DoR curve for each arm.

12.2.8. Pharmacokinetic and/or Pharmacodynamic Analyses

Pharmacokinetic analyses will be conducted on all patients who have received at least one dose of abemaciclib and have had samples collected (see Attachment 6).

Mean population PK parameters for abemaciclib in plasma (clearance, exposure, volume of distribution, and half-lives) and inter-individual PK variability will be computed using nonlinear mixed effects modelling (NONMEM). The current PK model for abemaciclib, which has been developed using plasma concentration data available from the Phase 1 Study JPBA, will be updated using the plasma data collected in this study. Covariate effects (such as age, weight, sex, and plasma protein levels) on the PK parameters of abemaciclib in plasma will also be investigated.

Likewise, and if warranted by the data, mean population PK parameters for fulvestrant and/or trastuzumab in plasma and inter-individual variability estimates will also be computed using nonlinear mixed-effect modelling implemented in NONMEM.

Pharmacodynamic and biomarker samples will be collected as specified in the Study Schedule (Attachment 1) and PK Sampling Schedule (Attachment 6). Refer to these attachments (including footnotes) for important information about these samples and their collection.

Pharmacodynamic data (such as neutrophil, lymphocyte, or platelet counts in blood, PFS, OS) collected in this study may also be analyzed by means of NONMEM and connected to the population PK model in a PK/Pharmacodynamics model.

Pharmacodynamic data from all patients undergoing pharmacodynamic assessments will be analyzed. The pharmacodynamic data will be combined and exploratory analyses will be conducted to determine if a relationship exists between plasma concentration and pharmacodynamic effect(s) in humans. Interpatient variability in human pharmacodynamic response will also be assessed.

The version of software used for the analysis will be documented and will meet the Lilly requirements of software validation.

12.2.9. Biomarker Analyses

The distributions of biomarkers will be summarized. Correlative analyses will be performed to investigate associations between biomarkers and clinical endpoints as deemed appropriate.

12.2.10. Health Outcome/Patient-Reported Outcome Analyses

Patient-reported outcomes are measured through paper versions of the following:

- mBPI-sf (modified Brief Pain Inventory, Short Form)
- EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life-Core 30)
- EQ-5D 5L (EuroQol 5-Dimension 5 Level)

The reason and number of missing and incomplete questionnaires/assessments by visit will be summarized for each instrument and study arm.

Further analysis details will be described in the SAP.

12.2.10.1. Pain Intensity and Assessment

Individual pain items on the mBPI-sf (that is, worst, least, average, and current pain) will be described using descriptive statistics by treatment arm. A mixed effects model, repeated measures model may be applied to compare between treatment arms, which will be adjusted for other covariates. Corresponding analyses will also be conducted for the mean of 7 pain interference with function items. If a patient does not complete Questions 5a through 5g on the BPI-sf, the mean score for the 7 pain interference items will be calculated based on those answered questions when at least 4 out of 7 questions were completed (that is, ≥50% of the questions were answered).

Pain analysis will be based on all randomized patients with at least 1 baseline BPI "worst pain" and one BPI "worst pain" score on Cycle 2 Day 1 or later.

The mBPI-sf will be administered at baseline prior to study drug dosing and the Cycle 1, Day 1 score will be treated as a baseline observation and the Day 1 score of each subsequent cycle will be attributed to the previous cycle. The mBPI-sf will be administered at treatment discontinuation and grouped with observations from the previous cycle.

12.2.10.2. Health-Related Quality of Life

EORTC QLQ-C30 instrument data will be scored as described in the EORTC scoring manual (Fayers et al. 2001). Descriptive statistics for each EORTC QLQ-C30 scale will be calculated and compared between arms.

12.2.10.3. Resource Utilization

Utilization data will be summarized descriptively by category across arms (for example, analgesic use, bisphosphonate use, transfusions, radiation, surgery, and hospitalization days), including a frequency table with tabular statistics. For categorical variables, frequency and the corresponding percentage will be derived and measures of central tendency and variability will be calculated for continuous variables by arm. Tests for differences in proportion between treatment groups and between response groups will be performed.

12.2.10.4. Health State Utility

The EQ-5D 5L data will be scored as described by van Hout and colleagues (van Hout et al. 2012). The index score is calculated from a set of item weights to derive a score of 0 to 1, with 1 representing the best health status. Geographic-specific weights will be described in the SAP. The VAS is scored from 0 (*worst imaginable health state*) through 100 (*best imaginable health state*) to represent the patient's self-report for each day. EQ-5D 5L responses for each item will be summarized by frequency and corresponding percentages. Descriptive statistics for the index and VAS will be calculated.

12.2.11. Safety Analyses

All safety summaries and analyses will be based upon the Safety Population as defined in Section 12.2.1.

Overall exposure to study drugs, the numbers of patients completing each cycle, and the dose intensity will be summarized using descriptive statistics. The number of patients with any dose adjustment will be presented for entire treatment period as well as for each cycle. The number of patients with dose reductions, dose delays, or dose omissions will also be summarized, as will the reasons for dose adjustments.

Preexisting conditions are defined as AEs that begin prior to the first dose of study drug.

A TEAE is defined as an event that first occurred or worsened in severity after baseline. Comparisons of preexisting conditions to on-treatment events at the LLT level will be used in the treatment-emergent computation.

An overall summary of AEs will be provided for AEs deemed by the investigator to be possibly related to study treatment, and repeated for events regardless of study treatment causality. Incidence rates of these events will be compared between treatment arms using Fisher's exact test.

The number of patients who experienced a TEAE, SAE, AE related to study treatment, died, or discontinued from the study due to an AE will be summarized by treatment.

Adverse events will be reported using the MedDRA dictionary. Investigators will report a verbatim AE term and a CTCAE v4.03 term and severity for all AEs. For analysis purposes, the following process will be used:

- The CTCAE v4 term reported by the investigator will be mapped to the MedDRA Preferred Term (PT) and System Organ Class (SOC) using the corresponding MedDRA Lower Level Term (LLT), unless the reported CTCAE term is 'Other – specify.'
- If the reported CTCAE term is 'Other – specify,' the MedDRA LLT, PT, and SOC centrally mapped from the verbatim AE term will be used.
- All listings and summaries will use the PT resulting from this process.

Laboratory and non-laboratory CTCAEs will be summarized by CTCAE term and maximum CTCAE grade, including the total for maximum Grade 3 and 4. These summaries will be provided for events deemed by the investigator to be possibly related to study treatment and repeated for events regardless of causality.

Reasons for death will be summarized separately for on-therapy and within 30 days of treatment discontinuation.

Hospitalizations and transfusions during the study treatment period or during the 30-day short-term follow-up period will be summarized by treatment group.

12.2.11.1. Dose-Limiting Toxicities for Arm A Safety Lead-In

For analyzing the safety and tolerability of the triplet combination of abemaciclib plus trastuzumab plus fulvestrant during the safety lead-in, a dose-limiting toxicity (DLT) is defined as an AE during Cycle 1 that is possibly related to abemaciclib and fulfills any one of the following criterion using the NCI CTCAE v 4.03:

- Grade 3 or 4 nonhematological toxicity except for nausea, vomiting, diarrhea, electrolyte disturbance, or alopecia
- Grade 3 or 4 nausea, vomiting, or electrolyte disturbance that persists more than 3 days despite maximal supportive intervention
- Grade 3 or 4 diarrhea that does not resolve to at least Grade 2 after 3 days of maximal supportive intervention
- Grade 4 hematological toxicity that persists more than 5 days
- Grade 3 or 4 thrombocytopenia with bleeding
- Febrile neutropenia
- Death related to toxicity

The patient population used for determination of DLTs will consist of patients who have met the minimum safety evaluation requirements of the study and/or who have experienced a DLT. Minimum safety requirements will be met if, during Cycle 1 of the safety lead-in, the patient receives at least 75% of the intended dose of study treatment and is observed for at least 28 days following the first dose of study drugs. Any patients enrolled in the safety lead-in cohort that do not meet the dosing criteria defined above in order to be considered complete may be replaced.

12.2.11.2. DLT-Equivalent Toxicity

A DLT-equivalent toxicity is defined as an AE that would have met the criteria for DLT in Section 12.2.11.1 if it had occurred during Cycle 1, but occurs in Cycle 2 or beyond during the monitoring for the safety lead-in period.

12.2.12. Interim Analyses

There are 2 planned interim analyses to evaluate the safety and tolerability of the combination of abemaciclib plus trastuzumab plus fulvestrant in patients enrolled to the safety lead-in for Part A; these analyses will take place when data from the first 6 and 12 qualified patients who complete 1 cycle have been obtained. These interim analyses will be performed by an assessment committee (AC) made up of Lilly members not involved in the day to day study conduct (the medical director, a Global Patient Safety [GPS] physician, and a statistician) plus the global principal investigators. In addition to the interim analyses for the safety lead-in, safety meetings will be held every 3 weeks with sites that have recruited and enrolled patients to Arm A during the safety lead-in period. These meetings will include the Lilly CRP, clinical trial manager, trial statistician, and GPS physician; additional personnel may participate as deemed appropriate.

If ≥2 of 6 patients or ≥4 of 12 patients in the safety lead-in experience a DLT or DLT-equivalent toxicity as defined in Sections 12.2.11.1 and 12.2.11.2, respectively, the dose of abemaciclib will be reduced to 100 mg for these patients and for all subsequent patients enrolled to Arm A. Even if the AC does not observe the specified number of DLTs or DLT-equivalent toxicities that would lead to dose reduction, Lilly may elect to reduce the dose of abemaciclib in Arm A if warranted by safety concerns. Safety data for Arm A will be continuously monitored during the safety lead-in period, and the decision to reduce the dose of abemaciclib may be made by Lilly at

any time. No protocol amendment will be needed to proceed with a lower dose level of abemaciclib in Arm A. If the dose of abemaciclib in Arm A is reduced to 100 mg, patients that initiated treatment at the 150-mg dose will be dose-reduced to 100 mg, and patients who started at the 150-mg abemaciclib dose will be replaced so that there are a total of 75 patients in Arm A with a starting dose of 100-mg abemaciclib. If the 100-mg dose is found to be intolerable, enrollment into Arm A will be discontinued.

In addition to the safety lead-in interim analyses for Arm A, there are 3 planned interim analyses for safety and 1 planned interim analysis for futility for all treatment arms in Study JPBZ. These interim analyses will be reviewed by the AC.

A safety interim analysis is planned after approximately 36 patients (a minimum of 12 patients in each of experimental arms A and B) have been treated for 1 cycle. There will be no prespecified rules for stopping the trial due to safety concerns. The AC members will review safety data at the interim analysis to determine whether there are sufficient safety concerns to justify the termination of study treatment and/or enrollment. Similar interim safety analyses will be performed after approximately 75 patients and after approximately 150 patients have been treated for 1 cycle (a minimum of 25 and 50 patients in experimental arms A and B).

The interim analysis for futility is planned after 75 PFS events have been observed. Futility for the interim analysis will be determined in terms of PFS. As guidance, an AC may recommend stopping the trial or closing an experimental arm for futility if the observed HR>1.3. The stopping guidance should be viewed as only guidance, not an absolute rule. The AC will consider all evidence, including safety and other efficacy parameters, in making this decision.

12.2.13. Subgroup Analyses

Subgroup analyses of PFS and OS will be performed for each of following potential prognostic subgroup variables, including:

- Number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer (2 to 3 versus more than 3)
- Measurable disease at baseline (yes versus no)
- Number of organs involved (1 versus 2 versus 3+)
- PgR status (positive versus negative)
- Baseline ECOG PS (0 versus 1)
- Age (<65 years versus ≥65 years)
- Region (North America, Europe, Asia, and Other)
- Race (Caucasian, Asian, and Other)

If a level of a factor consists of fewer than 10% of randomized patients, analysis within that level may be omitted. The final list of subgroup analyses will be provided in the SAP.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the potential risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue her participation in the trial.

The ICF will be used to explain the potential risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of study treatment.

As used in this protocol, the term "informed consent" includes all consent given by patients.

13.2. Ethical Review

Lilly or its representatives must approve all ICFs before they are used at the investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site[s].

The study site's ERB[s] should be provided with the following:

- the current IB or package labeling (for example, Patient Information Leaflet, Package Insert, or SPC) and updates during the course of the study
- the ICF
- relevant curricula vitae

13.3. Regulatory Considerations

This study will be conducted in accordance with:

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guideline (E6)
- applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a TPO.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting AEs and/or other trial-related data.

13.3.1. Investigator Information

Physicians with a specialty in oncology will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

13.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator will be chosen by Lilly to serve as the clinical study report coordinating investigator.

The Lilly responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

14. References

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Attachment 1. Protocol JPBZ Study Schedule

Study Schedule, Protocol I3Y-MC-JPBZ

Perform procedure as indicated.

Baseline Schedule	**Study Period**	Baseline	
	Visit	0	
	Approximate Visit Duration (days)	Up to 28	
	Relative day to Randomization	≤28	≤14

Procedure Category	**Procedure**			**Comments**
Study Entry /Enrollment	Informed consent form signed	X		Prior to conducting any protocol-specific tests / procedures
	Inclusion/exclusion evaluation		X	Collection of tumor tissue (newly obtained biopsy; otherwise archived tissue) is required for ALL patients for eligibility. Sites should confirm the availability of adequate tumor tissue with the pathological laboratory prior to randomization.
Medical History	Initial medical history/preexisting conditions		X	
	Historical illnesses		X	Including habits assessment of alcohol and tobacco use
Physical Examination	Physical exam		X	Including but not limited to height and weight
	Vital signs		X	Including blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status		X	
Tumor Assessment[a]	Tumor measurement (visible)	X		Photography of visible tumors (such as skin lesions) with ruler required, if applicable
	Radiologic imaging according to RECIST 1.1	X		Performed locally. <u>For patients with ONLY locoregional disease extension and NO measurable lesions on CAP CT scan</u>, MRI scan of the breast is performed in addition to other scans. Additionally, <u>for all patients</u>, CT or MRI scan of the chest, abdomen, and pelvis. CT scan is the best currently available and reproducible method to measure lesions selected for response assessment; it is recommended that CT imaging of the abdomen and pelvis be performed with IV contrast whenever possible. For patients with known hypersensitivity to CT contrast material, a CT scan of the chest without contrast and gadolinium-enhanced MRI of the abdomen and pelvis are encouraged.
	Bone scintigraphy	X		Performed locally. <u>For all patients</u>, bone scintigraphy performed as part of routine clinical care within 45 days before randomization is also acceptable.
	X-ray, CT scan with bone windows, or MRI	X		Performed locally. If CAP CT/MRI does <u>not</u> capture bone lesions, perform specific bone-directed imaging (X-ray, CT scan with bone windows, or MRI) at baseline. **<u>EXCEPTION:</u>** for the following patients, **NO** specific bone-directed imaging is required: • patients with **no** bone lesions at baseline • patients with measurable visceral disease <u>and</u> nonmeasurable bone lesions

Baseline Schedule		Study Period	Baseline		
		Visit	0		
		Approximate Visit Duration (days)	Up to 28		
		Relative day to Randomization	≤28	≤14	
Procedure Category	**Procedure**				**Comments**
Tumor Assessment[a]	Brain Gd-MRI		X		Required only for patients with treated brain metastases
Adverse Event Collection/CTCAE Grading			X		
Concomitant Medication Notation			X		
Health Outcomes	EORTC QLQ-C30 mBPI-SF EQ-5D 5L			X	Patients complete during screening and prior to extensive interaction with site staff. This is the first of two pre-abemaciclib collections (second is at Cycle 1 Day 1 prior to abemaciclib dose).
Lab/ Diagnostic Tests	Central hematology			X	Enrollment and treatment decisions may be based upon results of tests performed locally. If local laboratory tests are used for this purpose, then a duplicate specimen must be submitted to the central laboratory. Discrepancies between local and central laboratory that may have an impact on eligibility or treatment decisions will not be considered protocol deviations.
	Central chemistry			X	
	Cystatin C			X	Perform at central laboratory.
	Serum pregnancy test			X	Required only if postmenopausal status is due to ovarian suppression with a GnRH agonist or induced by radiation
	Local FSH and estradiol level			X	Required only for women <60 years with amenorrhea for at least 12 months and menopause due to radiation-induced ovarian suppression in order to confirm post-menopausal status
	Local ECG			X	Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
	Echocardiography or multiple-gated acquisition scanning (MUGA scan)		X		LVEF of 50% or higher is required at baseline for eligibility. Echocardiography or MUGA scan performed as part of routine clinical care within 45 days before randomization is also acceptable

Abbreviations: CAP = chest/abdomen/pelvis; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle stimulating hormone; Gd-MRI = gadolinium-enhanced magnetic resonance imaging; GnRH = gonadotropin-releasing hormone; IV = intravenous; MRI = magnetic resonance imaging; MUGA = multigated acquisition; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] If a patient requires palliative radiation at baseline, tumor assessments are to be conducted after end of radiotherapy and prior to randomization.

During Treatment Study Schedule		Study Treatment Period				
	Cycle / Visit	**1**	**2**	**3**	**4-X**	
	Approximate Visit Duration (days)	21	21	21	21	
	Relative day within a cycle	1	1	1	1	
Procedure Category	**Procedure**					**Comments**
Physical Examination	Physical exam	X	X	X	X	Including weight
	Vital signs	X	X	X	X	Including blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	X	X	X	X	
Archived Tumor Tissue		X				Block or 20 slides must be available prior to patient randomization.
Adverse Event Collection/CTCAE Grading		X	X	X	X	
Concomitant Medication Notation		X	X	X	X	
Lab/ Diagnostic Tests	Central hematology	X	X	X	X	For patients in the safety lead-in for Arm A, additional central hematology labs are required every week during Cycle 1. For all patients, central hematology labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local hematology labs may be drawn for treatment adjustment and patient management purposes.
	Central chemistry	X	X	X	X	Central chemistry labs may be drawn up to 3 days prior to Day 1 of each cycle. Additional local chemistry labs may be drawn for treatment adjustment and patient management purposes.
	Cystatin C	X	X	X	X	Perform at central laboratory.
	PK sampling	X	X	X	X	Refer to Attachment 6.
	Pharmacogenetic blood sample	X				Draw sample before patient is dosed on Cycle 1 Day 1
	Biomarker plasma sample	X	X			Draw sample before patient is dosed on Cycle 1 Day 1 and upon arrival at site on Cycle 2 Day 1
	Local ECG	X	X		X[a]	For patients in treatment Arms A and B, perform 2 to 4 hours after the abemaciclib dose on Cycle 1 Day 1, upon arrival at site on Cycle 2 Day 1, 2 to 4 hours after the abemaciclib dose on Cycle 4 Day 1. For patients in Arm C, perform at any time during visits. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Tumor Assessment	Echocardiography or multiple-gated acquisition scanning (MUGA scan)				X	Perform at Cycle 5 Day 1 (± 7 days). If LVEF is stable, repeat every 12 weeks starting with Cycle 9 Day 1 (± 7 days) and then every 24 weeks following discontinuation of trastuzumab. If LVEF on trastuzumab is <50%, refer to Section 10.3.2.2 for further monitoring guidance.

	Tumor measurement (visible)			X	X[b]	Skin lesions identified at baseline require repeat photographic images every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression. Photographic images may be taken more frequently based upon the discretion of the investigator or following the identification of new skin lesions post-baseline.
	Radiological imaging according to RECIST (CT scan/MRI)			X	X[b]	Performed locally. For patients with ONLY locoregional disease extension and NO measurable lesions out of breast on CAP CT scan, MRI scan of the breast is performed in addition to other scans. For all patients, imaging studies (CT scan or MRI of the chest, abdomen, and pelvis and breast MRI when applicable) will be repeated every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression. The same method of imaging used at baseline should be used for each subsequent assessment.
	Bone scintigraphy				X[c]	Performed locally. ONLY for patients with bone lesions identified on baseline bone scintigraphy, repeat bone scintigraphy every 24 weeks (± 3 business days). Additional bone scintigraphy should be considered if there is clinical suspicion of disease progression in bone. If a patient with bone lesions at baseline experiences a CR, bone scintigraphy should continue to be repeated every 24 weeks (± 3 business days) and until disease progression to detect new lesions. • Note: for patients with no bone lesions on baseline bone scintigraphy, bone scintigraphy should be performed ONLY if there is clinical suspicion of disease progression in bone, even if a CR is achieved. Importantly, RECIST v1.1 emphasizes that bone scintigraphy is not adequate to measure bone lesions; however, bone scintigraphy can be used to confirm the presence or disappearance of bone lesions.
	X-Ray, CT scan with bone windows, or MRI			X	X[b]	Performed locally. If CAP CT/MRI does not capture bone lesions, repeat specific bone-directed imaging (X-ray, CT scan with bone windows, or MRI) every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy, then every 9 weeks (± 3 business days), and within 14 days of clinical progression. **EXCEPTION:** for the following patients, **NO** specific bone-directed imaging is required: • patients with **no** bone lesions at baseline • patients with measurable visceral disease and nonmeasurable bone lesions The same imaging method used at baseline for bone lesions measurement is to be used during treatment period and follow-up.
Health Outcomes	EORTC QLQ-C30 mBPI-sf EQ-5D 5L	X	X	X	X	Patients complete prior to extensive interaction with site staff. On Cycle 1 Day 1, questionnaires must be administered prior to the first dose of study treatment (this will be the second of two screening PROs collected). Cycle 2 and later questionnaires should be administered on Day 1 of each cycle.
Study Drug[d]	Abemaciclib (LY2835219)	Take 150 mg every 12 hours on Days 1 through 21 of every cycle.				

Co-Administered Drug[d]	Trastuzumab	On label dosing: 8 mg/kg loading dose as a 90 minute IV infusion on Day 1 of Cycle 1 (of a 21 day cycle) then 6 mg/kg maintenance dose as a 30 minute IV infusion on Day 1 of Cycle 2 and beyond.	For patients already receiving trastuzumab at time of study entry, the trastuzumab dose on Cycle 1 Day 1 should be at least 21 days after the last dose administered prior to randomization. No loading dose of trastuzumab is required if the last dose of trastuzumab was within 4 weeks of Day 1 of Cycle 1. Loading dose of trastuzumab is required if the last dose of trastuzumab was administered more than 4 weeks prior to Day 1 of Cycle 1.
	Fulvestrant	On label dosing: 500 mg IM into buttocks slowly (1-2 minutes per injection) as two 5-mL injections on Days 1 15, and 29 (that is, Cycle 2 Day 8 [assuming no dose suspension for trastuzumab]), and every 4 weeks thereafter.	See Attachment 8 for more detail on the schedule for fulvestrant administration.
	Single-agent chemotherapy	Standard of care per physician's choice. Dosing per label.	Best supportive care alone, including palliative radiotherapy in the absence of chemotherapy is not permitted. T-DM1 or pertuzumab are not considered a single-agent chemotherapy option. Maintenance endocrine therapy (except fulvestrant) after single-agent chemotherapy, all concurrently with trastuzumab, is allowed.

During Treatment Study Schedule (concluded)

Abbreviations: CAP = chest/abdomen/pelvis; CR = complete response; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; IM = intramuscular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] ECG to be performed on Cycle 4 Day 1 but not in any subsequent cycle during Study Treatment Period.

[b] Procedure will not be performed on Day 1 of all Cycles 4-X. Rather, the procedure is to be performed every 6 weeks (± 3 business days) for 36 weeks from first dose of study therapy (regardless of treatment suspensions or delays), then every 9 weeks (± 3 business days), and within 14 days of clinical progression.

[c] Procedure will not be performed on Day 1 of all Cycles 4-X. Rather, the procedure is to be performed every 24 weeks (regardless of treatment suspensions or delays).

[d] See Section 9 and Table JPBZ.9.1 for details on treatment administration.

Post-Treatment Discontinuation Study Schedule

Study Period	Postdiscontinuation Short Term Follow-Up	Postdiscontinuation Long Term Follow-Up	
Visit	**801**	**802-X**	
Approximate Visit Duration (Days)	**30±5**	**Variable**	
Relative Day	**30**		
Procedure Category	**Procedure**		**Comments**
Physical Examination	Physical exam	X		Including weight
	Vital signs	X		Including blood pressure, pulse, respiratory rate, and temperature
	ECOG performance status	X		
Tumor Assessment	Tumor measurement (visible)	X	X	**ONLY For patients who are randomized and never received study treatment or those who discontinue study treatment without objectively measured PD,** continue to conduct tumor assessments approximately every 6 weeks for the first 36 weeks following randomization and thereafter approximately every 9 weeks until the patient has objective disease progression or until primary PFS analysis. After the patient has objective disease progression, photographic images are no longer required and the patient will continue with postdiscontinuation follow-up approximately every 9 weeks until the patient's death or overall study completion.
	Radiological imaging according to RECIST (CT scan/MRI)	X	X	The same method of imaging used at baseline should be used for each subsequent assessment. **ONLY For patients who are randomized and never received study treatment or those who discontinue study treatment without objectively measured PD**, continue to conduct tumor assessment approximately every 6 weeks for the first 36 weeks following randomization and thereafter approximately every 9 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until primary PFS analysis. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with postdiscontinuation follow-up approximately every 9 weeks until the patient's death or overall study completion.
	Bone scintigraphy	X	X	**ONLY for patients with bone lesions on baseline scintigraphy who are randomized and never received study treatment or those who discontinue study treatment without objectively measured PD,** continue to evaluate bone scintigraphy approximately every 24 weeks until objective disease progression or primary PFS analysis. EXCEPTION: for patients with **no** bone lesions on baseline bone scintigraphy, bone scintigraphy should be performed ONLY if there is clinical suspicion of disease progression in bone, even if a CR is achieved.

Post-Treatment Discontinuation Study Schedule	Study Period	Postdiscontinuation Short Term Follow-Up	Postdiscontinuation Long Term Follow-Up	
	Visit	**801**	**802-X**	
	Approximate Visit Duration (Days)	**30±5**	**Variable**	
	Relative Day	**30**		
Procedure Category	**Procedure**			**Comments**
	X-ray, CT scan with bone windows, or MRI	X	X	**ONLY For patients who are randomized and never received study treatment or those who discontinue study treatment without objectively measured PD, focused studies are performed (EXCEPT** for patients with **no** bone lesions at baseline and patients with measurable visceral disease and nonmeasurable bone lesions). To be repeated approximately every 6 weeks for the first 36 weeks following randomization and thereafter approximately every 9 weeks by the same method used at baseline and throughout the study until the patient has objective disease progression or until primary PFS analysis. After the patient has objective disease progression, radiologic tests are no longer required and the patient will continue with postdiscontinuation follow-up approximately every 9 weeks until the patient's death or overall study completion.
Survival Information		X	X	Although preferable to collect during a clinic visit, survival information may be collected by contacting the patient or family directly (for example, via telephone) if no procedures required. This should be collected at minimum every 90 days if no other procedures are performed. Additional long-term follow-up data collection will include postdiscontinuation anticancer therapies.
Adverse Events Collection/ CTCAE Grading		X	X	After Visit 801, only study protocol or drug-related events are reported. If a patient has ongoing AE or SAE possibly related to study drug (not co-administered drug) (for instance, abnormal electrolytes), the patient should be followed until the event is resolved, the event is no longer considered to be drug-related, the event becomes stable or returns to baseline, a new treatment is initiated for the patient, or the patient dies or is lost to follow-up. Any subsequent follow-up(s) for AEs will be no more than 30 days ± 5 days in duration.
Concomitant Medication Notation		X		

Post-Treatment Discontinuation Study Schedule

Study Period	Postdiscontinuation Short Term Follow-Up	Postdiscontinuation Long Term Follow-Up	
Visit	**801**	**802-X**	
Approximate Visit Duration (Days)	**30±5**	**Variable**	
Relative Day	**30**		
Procedure Category / **Procedure**			**Comments**
Lab/Diagnostic Tests — Central hematology	X		
Central chemistry	X		
Cystatin C	X		Perform at central laboratory.
Biomarker plasma sample	X		Draw sample for all patients
ECG	X		Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection
Biomarker Tests — Tumor tissue collection	X		Collect tumor tissue from new biopsy if feasible and ONLY for patients discontinuing due to PD
Health Outcomes — EORTC QLQ-C30 mBPI-sf EQ-5D 5L	X		

Abbreviations: AE = adverse event; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-BR23 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast cancer; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D 5L = EuroQol 5-Dimension 5 Level; MRI = magnetic resonance imaging; PD = progressive disease; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAEs = serious adverse events.

Study Schedule for the Continued Access Period only	Study Period	Patients on Study Treatment	Continued Access Period Follow-up	
	Cycle	X	Follow-up[a]	
	Visit	501-5XX	901	
	Approximate Visit Duration (days)	21	30	
	Relative day within a cycle	1		
Procedure Category	**Procedure**			**Comments**
Adverse Event Collection/CTCAE Grading		X	X	Data on SAEs that occur before the end of trial will be stored in the collection database and the Lilly safety system
Study Treatment	Abemaciclib	X		Only patients assigned to abemaciclib at randomization and receiving clinical benefit will continue to receive abemaciclib during the continued access period. Abemaciclib is to be administered orally every 12 hours on Days 1 through 21 of each cycle. Patients who were assigned to single-agent chemotherapy plus trastuzumab cannot crossover to receive abemaciclib.
	Trastuzumab	X		Patients receiving clinical benefit will continue to receive trastuzumab and/or fulvestrant during the continued access period. Trastuzumab is to be administered as a 6 mg/kg 90 minute IV infusion on Day 1 of a 21 day cycle. If the initial dose of trastuzumab was well tolerated, the subsequent doses can be administered as a 30-minute infusion. For reloading of trastuzumab, take into account dose-adjustment guidance[b]. Fulvestrant is to be administered 500 mg IM into buttocks once monthly. Standard-of-care chemotherapy administered according to product label.
	Fulvestrant	X		
	Single-agent standard-of-care chemotherapy	X		

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IM = intramuscular; IV = intravenous; OS = overall survival; SAEs = serious adverse events; SPC = Summary of Product Characteristics.

[a] The continued access period begins after study completion (that is, after final OS analysis) and ends at the end of trial (that is, the last patient visit).

[b] See Section 2.2 (Important Dosing Considerations) of the United States package insert (Herceptin [trastuzumab] package insert 2016) or Section 4.2 (Posology and Method of Administration) of the SPC (Herceptin [trastuzumab] SPC 2016).

Attachment 2. Protocol JPBZ Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]:	**Clinical Chemistry[a]:**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume (MCV)	Total protein
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils, segmented and bands	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT)
Monocytes	Aspartate aminotransferase (AST)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Calcium
	Albumin
	Renal Panel[a]
	Cystatin-C
	Follicle stimulating hormone (FSH) levels[b,c]
	Serum pregnancy test[b,d]
	Estradiol level[b,c]

Abbreviations: GnRH = gonadotropin-releasing hormone; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated (central) laboratory

b Local or investigator-designated laboratory.

c To be performed at baseline in order to establish eligibility only for women <60 years and amenorrheic for at least 12 months.

d To be performed at baseline to establish eligibility if postmenopausal status is due to ovarian suppression with a GnRH agonist or induced by radiation.

Attachment 3. Protocol JPBZ Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow up with patients in consultation with the Lilly clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Anti-actin antibody[a]**
GGT	**Anti-smooth muscle antibody[a]**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Protocol JPBZ ECOG Performance Status

ECOG Performance Status

Activity Status	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 a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead.

Source: Oken et al. 1982.

Attachment 5. Protocol JPBZ RECIST Criteria 1.1

Response and progression will be evaluated in this study using the international criteria proposed by the New Response Evaluation Criteria in Solid Tumors (RECIST): Revised RECIST Guideline (version 1.1; Eisenhauer et al. 2009).

Measurability of Tumor at Baseline

Tumor lesions/lymph nodes will be categorized at baseline as measurable or nonmeasurable. Measurable disease is defined by the presence of at least 1 measurable lesion.

Measurable

Tumor lesions: Measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (slice thickness ≤5 mm)
- 10 mm caliper measurement by clinical exam (non-measurable lesions if cannot be accurately measured with calipers)
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan thickness recommended to be ≤5 mm).

Nonmeasurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitis involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measureable by reproducible imaging techniques.

Special Considerations for Lesion Measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI, can be considered measurable lesions if the soft tissue component meets the definition of measurability.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable)
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability. If noncystic lesions are presented in the same patients, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated at a previously irradiated area, or in an area subjected to other loco-regional therapy, are non-measurable unless there has been demonstrated progression in the lesion.

Baseline Documentation of Target and Non-Target Lesion

Target Lesions

When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Non-nodal Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and can be reproduced in repeated measurements. Measurable lymph nodes are target lesions if they meet the criteria of a short axis of ≥15 mm by CT scan. All measurements are to be recorded in the electronic case record form (eCRF) in millimeters (or decimal fractions of centimeters [cm]).

Nontarget Lesions

All other lesions (or sites of disease) are identified as nontarget lesions (chosen based on their representativeness of involved organs and the ability to be reproduced in repeated measurements) and should be recorded at baseline. Measurement of these lesions are not required but should be followed as 'present,' 'absent,' or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF (for example, multiple liver metastases recorded as 1 liver lesion).

Lymph nodes with short axis ≥10 mm but <15 mm should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and are not recorded or followed.

Specifications by Methods of Measurement

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is

should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessed by clinical exam.

An adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. If prior to enrollment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) should be used to evaluate the patient at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (for example, skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT and MRI: CT scan is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is ≤5 mm. When CT scan have slice thickness >5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (for example, for body scans). If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

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

Tumor Markers: Tumor markers alone cannot be used to assess tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete response (CR). Specific guidelines for both prostate-specific antigen (PSA) response (in recurrent prostate cancer) and CA-125 response (in recurrent ovarian cancer) have been published.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete response (CR) in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (for example, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

Pet Scan (FDG-PET, PET CT): PET is not recommended for lesion assessment. If a new lesion is found by PET, another assessment must be done by CT, unless the PET CT is of diagnostic quality. If CT is done to confirm the results of the earlier PET scan, the date of progression must be reported as the earlier date of the PET scan.

Bone Scan: If lesions measured by bone scan are reported at baseline, it is necessary to repeat the bone scan when trying to identify a complete response (CR) or partial response (PR) in target disease or when progression in bone is suspected.

Response Criteria

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (including the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.

For equivocal findings of progression (for example, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

Not Evaluable: When an incomplete radiologic assessment of target lesions is performed or there is a change in the method of measurement from baseline that impacts the ability to make a reliable evaluation of response.

Evaluation of Nontarget Lesions

Complete Response: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be non-pathological or normal in size (<10mm short axis).

Non-CR/ non-PD: Persistence of 1 or more nontarget lesions and/or maintenance of tumor marker level above the normal limits.

Progressive Disease: Unequivocal progression of existing nontarget lesions. The appearance of 1 or more new lesions is also considered progression.

Not Evaluable: When a change in method of measurement from baseline occurs and impacts the ability to make a reliable evaluation of response.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. The Best Overall Response will be calculated via an algorithm using the assessment responses provided by the investigator over the course of the trial.

Time Point Response

It is assumed that at each protocol-specified time point, a response assessment occurs. (When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.) Table 1 provides a summary of the overall response status calculation at each time point for patients who have *measurable disease* at baseline.

Table 1. Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response; PR = partial response; SD = stable disease.; PD = progressive disease; NE = inevaluable.

Table 2 is to be used when patients have *nonmeasurable* disease only.

Table 2. Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response; PD = progressive disease ; NE = inevaluable.

[a] non-CR/non-PD is preferred over SD for nontarget disease.

Frequency of Tumor Re-Evaluation

A baseline tumor evaluation must be performed within 4 weeks before patient begins study treatment. Frequency of tumor re-evaluation while on and adapted to treatment should be protocol-specific and adapted to the type and schedule of treatment. In the context of Phase 2 studies where the beneficial effect therapy is not known, follow-up every 6-8 weeks is reasonable. Normally, all target and non-target sites are evaluated at each assessment using the same method. However, bone scintigraphy may need to be repeated only when CR is identified in target disease or when progression in bone is suspected.

Confirmatory Measurement/Duration of Response

Confirmation:
The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. The confirmation of response is particularly important in *nonrandomized trials* where response (CR/PR) is the primary end point. In this setting, to be assigned a status of PR/CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. To confirm a response of CR, a full assessment of all target and nontarget lesions that were present at baseline must occur, including those measured by bone scan. To confirm a PR or SD, a full assessment of target lesions that were present at baseline must occur; assessment of nontargets is not required.

However, in *randomized trial* (Phase 2 or 3) or studies where SD or progression is the primary endpoints, confirmation of response is not required. But, elimination of the requirement may increase the importance of central review to protect against bias, in particular of studies which are not blinded.

In the case of SD, follow-up measurements must have met the SD criteria at least once after start of treatment at a minimum interval not less than 6 weeks measured from first dose.

Duration of Overall Response
The duration of overall response is measured from the time measurement criteria are first met for CR or PR (whichever is first recorded) until the first date that disease is recurrent or objective progression is observed (taking as reference for PD the smallest measurements recorded on study).

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

Duration of Stable Disease
Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for objective progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, that is the reference for calculation of PD).

Independent Review of Response and Progression

When objective response (CR + PR) is the primary end point, and when key drug development decisions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomized trial, ideally reviewers should be blinded to treatment assignment.

Attachment 6. Protocol JPBZ Pharmacokinetic Sampling Schedule

Pre-abemaciclib dose samples are requested to be taken immediately before the dose. Aberrations to specified sampling times will not be considered protocol deviations as long as the samples are taken and the actual sampling time is recorded. For abemaciclib, the date, time, and amount of each dose for 3 days prior to PK sampling and the day of PK sampling must be recorded on the appropriate form. For trastuzumab, it is essential that the dose amount and exact infusion start and stop times (actual clock readings) are recorded. For fulvestrant, record the dose amount and start time of the intramuscular injection. The exact time of collection of each venous blood sample will be based on the clock used to record infusion times. It is essential that the pharmacokinetic blood samples not be withdrawn from the same site as the drug infusion.

In the event of suspending dosing for any component of study treatment due to toxicity on a day when a PK sample is scheduled, the PK sample prior to when the dose would have normally occurred should still be taken. In these cases, the PK sample that was to be taken after drug administration should be omitted on that day.

Arm A

Cycle (C) and Day (D)	Dose Abemaciclib	Dose Trastuzumab	Dose Fulvestrant	Abemaciclib Plasma PK Sample Number	Trastuzumab Serum PK Sample Number	Fulvestrant Plasma PK Sample Number	PK Sampling Time[a]
C1D1	X	X	X	1	1	1	Pre-abemaciclib dose (0 h)
C1D1				2	2		Immediately ***after end*** of trastuzumab infusion[b]
C1D15	X		X	3		2	Pre-fulvestrant dose (0 h)
C2D1	X	X		4	3		Pre-trastuzumab dose (0 h)
C2D1				5	4		Immediately ***after end*** of trastuzumab infusion[b]
C2D8	X		X	6		3	Pre-fulvestrant dose (0 h)
C3D1	X	X		7	5		Pre-trastuzumab dose (0 h)
C3D1				8	6		Immediately ***after end*** of trastuzumab infusion[b]
C3D15	X		X	9		4	Pre-fulvestrant dose (0 h)
C4D1	X	X		10	7		Pre-trastuzumab dose (0 h)
C4D1				11	8		Immediately ***after end*** of trastuzumab infusion[b]
C5D1	X	X	X	12	9	5	Pre-trastuzumab dose (0 h)
C5D1				13	10		Immediately ***after end*** of trastuzumab infusion[b]

Abbreviations: h = hour; min = minute; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites concentrations in plasma. A second set of samples of approximately 2 mL of whole blood will be drawn for measurement of trastuzumab concentrations in serum. A third set of samples of approximately 2 mL of venous blood will be drawn for measurement of fulvestrant concentrations in plasma.

[b] These samples should be taken as soon as possible, up to 5 minutes, after the end of the infusion.

Arm B

Cycle (C) and Day (D)	Dose Abemaciclib	Dose Trastuzumab	Abemaciclib Plasma PK Sample Number	Trastuzumab Serum PK Sample Number	PK Sampling Time[a]
C1D1	X	X	1	1	Pre-abemaciclib dose (0 h)
C1D1			2	2	Immediately ***after end*** of trastuzumab infusion[b]
C2D1	X	X	3	3	Pre-trastuzumab dose (0 h)
C2D1			4	4	Immediately ***after end*** of trastuzumab infusion[b]
C3D1	X	X	5	5	Pre-trastuzumab dose (0 h)
C3D1			6	6	Immediately ***after end*** of trastuzumab infusion[b]
C4D1	X	X	7	7	Pre-trastuzumab dose (0 h)
C4D1			8	8	Immediately ***after end*** of trastuzumab infusion[b]
C5D1	X	X	9	9	Pre-trastuzumab dose (0 h)
C5D1			10	10	Immediately ***after end*** of trastuzumab infusion[b]

Abbreviations: h = hour; min = minute; PK = pharmacokinetic.

[a] Samples of approximately 2 mL of whole blood will be drawn for measurement of abemaciclib and its metabolites concentrations in plasma. A second set of samples of approximately 2 mL of whole blood will be drawn for measurement of trastuzumab concentrations in serum.

[b] These samples should be taken as soon as possible, up to 5 minutes, after the end of the infusion.

Attachment 7. Protocol JPBZ Sampling Summary

This table provides estimates of the maximum number of samples, volumes for all sampling, and tests required for each patient during the study. More samples could be required in the case of retests, additional health monitoring (if needed), or for patients continuing treatment beyond the protocol-specified number of cycles in the study. Fewer samples may actually be taken (for example, if the patient discontinues from the study early).

Protocol I3Y-MC-JPBZ Sampling Summary[a]

Sample Type/Purpose		Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Blood				
Study qualification (*Baseline*)	Chemistry	2.5 mL	1	2.5 mL
	Hematology	2.0 mL	1	2.0 mL
Health monitoring	Chemistry	2.5 mL	11	27.5 mL
	Hematology	2.0 mL	11	22 mL
Drug concentration (*Arm A*)		2 mL	28	56 mL
Drug concentration (*Arm B*)		2 mL	20	40 mL
Tailoring biomarkers, pharmacogenetic		10 mL	1	10 mL
Tailoring biomarkers, serum and/or plasma		10 mL	3	30 mL
Hepatic monitoring[b]		3 - 30 mL	-	-
Total blood volume		-	-	190 mL
Tumor tissue Tailoring biomarkers, tissue		Refer to the study schedule (Attachment 1) for details and frequency of sampling.		

a Covers Cycles 1 through 10, and 801

b Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with the designated clinical research physician.

Attachment 8. Protocol JPBZ Dosing Schedule for Study Arm A

The following dosing schedule assumes oral administration Q12H of abemaciclib on Days 1 through 21 of each cycle and in the absence of treatment suspension or delay:

Cycle	Day 1	Day 8	Day 15
1	fulvestrant/trastuzumab		fulvestrant
2	trastuzumab	fulvestrant	
3	trastuzumab		fulvestrant
4	trastuzumab		
5	fulvestrant/trastuzumab		
6	trastuzumab	fulvestrant	
7	trastuzumab		fulvestrant
8	trastuzumab		
9	fulvestrant/trastuzumab		
10	trastuzumab	fulvestrant	
11	trastuzumab		fulvestrant
12	trastuzumab		
13	fulvestrant/trastuzumab		
14	trastuzumab	fulvestrant	
15	trastuzumab		fulvestrant
16	trastuzumab		
17	fulvestrant/trastuzumab		
18	trastuzumab	fulvestrant	
19	trastuzumab		fulvestrant
20	trastuzumab		
21	fulvestrant/trastuzumab		
22	trastuzumab	fulvestrant	
23	trastuzumab		fulvestrant
24	trastuzumab		

Attachment 9. Protocol JPBZ Inducers and Strong Inhibitors of CYP3A

The information in this table is provided for guidance to investigators and does not preclude the use of these medications if clinically indicated.

Strong Inducers of CYP3A
Carbamazepine
Dexamethasone[a]
Phenobarbital/phenobarbitone
Phenytoin
Rifapentine
Rifampin
Rifabutin
St John's wort

Moderate Inducers of CYP3A
Bosentan
Lesinurad
Modafinil
Primidone
Telotristat ethyl

Strong Inhibitors of CYP3A
Aprepitant
Ciprofloxacin
Clarithromycin
Conivaptan
Diltiazem
Erythromycin
Fluconazole
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Troleandomycin
Verapamil

[a] Important note: All patients may receive supportive therapy with dexamethasone, preferably ≤7 days, if clinically indicated.

Attachment 10. Protocol JPBZ CTCAE 4.03 Definitions for Diarrhea and ILD/Pneumonitis

Diarrhea will be evaluated in this study using the criteria proposed by Common Terminology Criteria for Adverse Events (CTCAE) v4.0 revised: CTCAE 4.03-June 14, 2010: Gastrointestinal disorders.

Gastrointestinal Disorders					
Grade					
Adverse Event	**1**	**2**	**3**	**4**	**5**
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: a disorder characterized by frequent and watery bowel movements					

Abbreviation: ADL = Activities of Daily Living.

Interstitial lung disease/pneumonitis will be evaluated in this study using the criteria proposed by CTCAE v4.0 revised: CTCAE 4.03–June 14, 2010: Respiratory, thoracic, and mediastinal disorders.

Respiratory, Thoracic, and Mediastinal Disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
ILD/Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: a disorder characterized by inflammation focally or diffusely affecting the lung parenchyma					

Abbreviations: ADL = Activities of Daily Living; ILD = interstitial lung disease.

Attachment 11. Protocol JPBZ Amendment (f) Summary monarcHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

Overview

Protocol I3Y-MC-JPBZ has been amended. The new protocol is indicated by amendment (f) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- The Rationale for Amendment (f) was added as Section 5.6.
- An error was corrected in the table in Special Hepatic Safety Data Collection (Section 10.3.3.1) to align with current guidance.

Minor typographical and formatting edits were made throughout the document for clarity and consistency.

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