Official Title: A Phase II, Multicenter, Randomized Study To Compare The Efficacy Of Venetoclax Plus Fulvestrant Versus Fulvestrant In Women With Estrogen Receptor-Positive, Her2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy

NCT Number: NCT03584009

Document Date: Protocol Version 4: 16-Oct-2020

PROTOCOL

TITLE: **A PHASE II, MULTICENTER, RANDOMIZED STUDY TO COMPARE THE EFFICACY OF VENETOCLAX PLUS FULVESTRANT VERSUS FULVESTRANT IN WOMEN WITH ESTROGEN RECEPTOR–POSITIVE, HER2–NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO EXPERIENCED DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER CDK4/6 INHIBITOR THERAPY**

PROTOCOL NUMBER:	WO40181
VERSION NUMBER:	4
EUDRACT NUMBER:	2017-005118-74
IND NUMBER:	137088
TEST PRODUCT:	Venetoclax (RO5537382)
NCT NUMBER	*NCT03584009*
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 26 January 2018
DATES AMENDED:	Version 2 (United Kingdom): 21 May 2018 Version 3: 19 September 2018 Version 4: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
16-Oct-2020 14:36:47	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 4
RATIONALE

Protocol WO40181 has been amended to address recent data available from the primary analysis. At the primary analysis of this study (clinical cut-off date of 5 August 2020), a higher proportion of deaths was observed in the venetoclax plus fulvestrant arm compared with the fulvestrant arm. Additionally, the venetoclax plus fulvestrant arm did not demonstrate a numerical improvement in the primary endpoint of clinical benefit rate (CBR) or the secondary endpoint of progression-free survival (PFS) compared with the fulvestrant arm. Changes to the protocol, along with a rationale for each change, are summarized below:

- The study rationale and benefit-risk assessment has been updated to indicate that, based on the results of the primary analysis, it is no longer considered appropriate for patients in this study to receive venetoclax. As of 8 October 2020, all active patients in the venetoclax plus fulvestrant arm of the study will be requested to discontinue the venetoclax treatment immediately, and will be given the option to continue fulvestrant treatment alone (Section 1.4).
- Language regarding the study design, study treatment, and treatment interruption has been updated to reflect the immediate discontinuation of venetoclax treatment (Sections 3.1, 4.3.2.1, 5.1.3.2, Appendix 1).
- The frequency of survival follow-up has been increased from approximately every 6 months to approximately every 3 months or more frequently after treatment discontinuation, to enhance safety data collection (Sections 3.1, 4.6.1, Appendix 1). Furthermore, language has been added to clarify that new anti-cancer therapy after study drug discontinuation should be reported once known (Appendix 1).

Additional changes made to the protocol are as follows:

- On the basis of the updated fulvestrant Summary of Product Characteristics, language pertaining to the use of contraception has been updated to indicate that contraception should be used for up to 2 years after the last dose of study drug, or based on local prescribing information for fulvestrant (Sections 4.1.1, 5.1.1.5).
- Adverse events of special interest for the study have been modified to remove hepatitis B reactivation (Section 5.2.3)
- The Medical Monitor has been changed and emergency medical contact information updated accordingly (Section 5.4.1).
- The reference safety information document for venetoclax has been updated to Venetoclax Investigator's Brochure for solid tumour studies (Section 5.7).
- Language regarding the statistical considerations for primary and secondary efficacy endpoints has been amended to specify the calculation of the 95% confidence interval (CI) for CBR estimate, and 95% CI for the Cox proportional hazards model for PFS, following reporting conventions (Sections 6.4.1, 6.4.2.1).

- The patient-reported outcome analysis has been updated and clarified the definition of clinically meaningful changes in European Organisation for Research and Treatment of Cancer QLQ-C30 scores (Section 6.7.1).
- Language has been added to indicate that the study will comply with applicable local, regional, and national laws (Section 8.1).
- A new section has been added to describe the implementation of a system to manage the quality of the study (Section 9.3), and subsequent sections were renumbered accordingly.
- Language has been revised to clarify that data posting will be available in clinical trial registries and to clarify that redacted Clinical Study Reports will be available upon request (Section 9.6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED STUDY TO COMPARE THE EFFICACY OF VENETOCLAX PLUS FULVESTRANT VERSUS FULVESTRANT IN WOMEN WITH ESTROGEN RECEPTOR–POSITIVE, HER2–NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO EXPERIENCED DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER CDK4/6 INHIBITOR THERAPY**
PROTOCOL NUMBER:	WO40181
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TEST PRODUCT:	Venetoclax (RO5537382)
MEDICAL MONITOR:	[redacted], *M.D., Ph.D.*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the contract research organization (CRO).

PROTOCOL SYNOPSIS

TITLE:	**A PHASE II, MULTICENTER, RANDOMIZED STUDY TO COMPARE THE EFFICACY OF VENETOCLAX PLUS FULVESTRANT VERSUS FULVESTRANT IN WOMEN WITH ESTROGEN RECEPTOR–POSITIVE, HER2–NEGATIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO EXPERIENCED DISEASE RECURRENCE OR PROGRESSION DURING OR AFTER CDK4/6 INHIBITOR THERAPY**
PROTOCOL NUMBER:	WO40181
VERSION NUMBER:	4
EUDRACT NUMBER:	2017-005118-74
IND NUMBER:	137088
NCT NUMBER	*NCT03584009*
TEST PRODUCT:	Venetoclax (RO5537382)
PHASE:	Phase II
INDICATION:	Estrogen receptor-positive (ER+)/human epidermal growth factor receptor (HER2)-negative locally advanced or metastatic breast cancer
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy of venetoclax (GDC-0199; ABT199) in combination with fulvestrant compared with fulvestrant alone in women with estrogen receptor-positive (ER+), human epidermal growth factor receptor (HER2)-negative, locally advanced breast cancer not amenable to surgical or local therapy with curative intent or with metastatic breast cancer (MBC) who experienced disease recurrence or progression during or after being treated with cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy for at least 8 weeks prior to progression. Specific objectives and corresponding endpoints for the study are outlined below.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of venetoclax in combination with fulvestrant compared with fulvestrant alone	• Clinical benefit defined as CR, PR, or SD lasting ≥24 weeks from randomization in patients with measurable disease at baseline, as determined by the investigator according to RECIST v1.1.
Secondary Efficacy Objective:	
• To evaluate the efficacy of venetoclax in combination with fulvestrant compared with fulvestrant alone	• PFS, defined as the time from randomization to the first occurrence of disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first • Objective response, defined as CR or PR, as determined by the investigator according to RECIST v1.1 • DOR, defined as time from the first occurrence of a documented objective response to the time of the first documented disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause
Safety Objective:	
• To evaluate safety and tolerability of venetoclax in combination with fulvestrant compared with fulvestrant alone	• Frequency and severity of adverse events, focusing on SAEs, AESI, and AEs leading to drug and/or study discontinuation
Pharmacokinetic Objectives:	
• To assess the pharmacokinetics of venetoclax and fulvestrant following administration of venetoclax in combination with fulvestrant	• Plasma concentrations of venetoclax and fulvestrant at specified timepoints
• To assess potential drug-drug interactions between venetoclax and fulvestrant	• Plasma concentrations or PK parameters of venetoclax and fulvestrant given in combination compared with these agents given alone (based on historical data)
Biomarker Objectives:	
• To evaluate predictive, prognostic, and pharmacodynamic biomarkers in tumor tissue and plasma associated with disease activity, response to treatment, or resistance to venetoclax in combination with fulvestrant	• Baseline BCL-2 protein levels as measured by IHC correlating with clinical response measures • Expanded biomarkers (see Table 2) measured at baseline, on-treatment, and at end of treatment relative to clinical response measures

Table 1 Objectives and Corresponding Endpoints (cont.)

PRO Objectives:	
• To evaluate PROs of function, disease/treatment-related symptoms, and GHS/overall HRQoL associated with venetoclax in combination with fulvestrant compared with fulvestrant alone • To evaluate and compare PROs of disease-related pain in venetoclax in combination with fulvestrant compared with fulvestrant alone	• Mean and mean changes from baseline scores in functional (i.e., role, physical, emotional, and social), disease/treatment-related symptoms, and GHS/HRQoL by cycle as assessed by the scales (Questions 29 and 30) of the EORTC QLQ-C30 • Change in baseline pain score as assessed by the pain scale (Questions 9 and 19) of EORTC QLQ-C30

AEs = adverse events; AESI = adverse events of special interest; BCL-2 = B-cell lymphoma 2; CR = complete response; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; IHC = immunohistochemistry; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAEs = serious adverse events; SD = stable disease.

Study Design

Description of Study

This is a Phase II, multicenter, open-label, randomized study to compare the efficacy of venetoclax in combination with fulvestrant compared with fulvestrant alone in women with ER+, HER2-negative, inoperable, locally advanced or MBC who experienced disease recurrence or progression during or after treatment with CDK4/6i therapy for at least 8 weeks. Approximately 100 patients from approximately 40 centers globally will be enrolled. Fresh tumor tissue (or archival tissue) will be collected during screening from all patients to confirm and determine HER2, estrogen receptor (ER), and B-cell lymphoma 2 (BCL-2) status. ER status will be defined by using immunohistochemistry (IHC) per the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) criteria, and HER2 negativity will be defined per the ASCO/CAP criteria. BCL-2 expression will be assessed by a central laboratory using the Ventana BCL-2 IHC assay. BCL-2 high is defined as $\geq$50% of tumor cells stained with an intensity of IHC 2^+ or 3^+, and BCL-2 low is defined as $\geq$50% stained with an intensity of IHC 0 or 1^+ and $<$50% stained an intensity of IHC 2^+ or 3^+.

Patients who do not initially meet all eligibility criteria may be rescreened once within 2 weeks, given that the reason for screening failure was not ER or HER-2 status. Each patient must be re-consented before re-screening occurs.

Central laboratory assessments will occur prior to randomization. Patients must have measurable disease (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]) locally advanced or metastatic disease with at least one evaluable lesion. Detailed information is listed in the inclusion and exclusion criteria. Locally advanced disease must not be amenable to resection or other local therapy with curative intent. Patients will be randomized in a 1:1 ratio to receive venetoclax in combination with fulvestrant or fulvestrant alone. Randomization will be stratified between the two arms on the basis of BCL-2 status and one versus two lines of prior therapy in the locally advanced/metastatic setting.

Study Treatment

- **Venetoclax arm:** venetoclax 800-mg tablet (8 $\times$ 100-mg tablet formulation) taken orally (PO) once a day (QD) beginning on Cycle 1 Day 1 and fulvestrant 500 mg administered as two 250-mg intramuscular (IM) injections on Cycle 1 Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle.

- **Control arm:** fulvestrant 500 mg administered as two 250-mg IM injections on Cycle 1 Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle. No crossover to the venetoclax arm is permitted. .

Tumor assessments will be conducted for all patients at screening and at every 8 weeks (±5 days) from the date of randomization until Week 24 (±5 days) and every 12 weeks (±5 days) thereafter. Tumor assessments will be conducted regardless of dose delays or early discontinuation until investigator-assessed disease progression (as specified below), the predefined end of the study, or until death, whichever occurs first.

Study treatment for each patient will continue until disease progression, unacceptable toxicity, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Diagnosis of disease progression should be supported by radiology assessments as per RECIST v1.1. All patients who are discontinued from all study treatment will return for a study drug discontinuation visit 28 days (+3 days) after the last dose of study treatment.

Patients who are discontinued from study treatment for reasons other than disease progression and have started follow-on treatment will be followed for survival approximately every *3 months, or more frequently,* until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are discontinued from study treatment for reasons other than disease progression and have not started follow-on treatment will be followed for disease status every 8 weeks (±5 days) from the date of randomization until Week 24 (±5 days) and then every 12 weeks (±5 days) thereafter until disease progression, death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

After disease progression, patients will be followed for survival and subsequent anti-cancer therapies approximately every *3 months, or more frequently,* until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Safety will be evaluated by monitoring the overall safety events, including all adverse events identified through physical examinations, and assessments of vital signs and laboratory test results. Such events will be graded by the investigators with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). Safety assessments from laboratory test results will include monitoring of hematology and blood chemistry.

As of 8 October 2020, all active patients in the venetoclax plus fulvestrant arm of the study will be requested to discontinue the venetoclax treatment immediately, and will be given the option to continue fulvestrant treatment alone.

Number of Patients

Approximately 100 patients from approximately 40 centers globally will be enrolled.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Female and ≥18 years of age at time of signing Informed Consent Form
- Signed Informed Consent Form
- Histological or cytological confirmation of ER+ invasive carcinoma of the breast with the following tumor molecular characteristics:
  - Documented ER+ defined by using IHC per ASCO/CAP criteria
  - Documented HER2-negative per ASCO/CAP criteria. Patients who were originally diagnosed with HER2-positive breast cancer that converted to HER2-negative MBC are NOT eligible to take part in this study.
  - Evaluable sample for BCL-2 IHC value at the time of screening
- Evidence of metastatic or locally advanced disease not amenable to surgical or local therapy with curative intent
- Be either:

  Postmenopausal, defined as:

- Age ≥ 60 years OR,
- Age < 60 years AND have undergone bilateral oophorectomy, medically confirmed ovarian failure OR,
- Age < 60 years AND have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have serum levels of estradiol and follicle-stimulating hormone within the laboratory's reference range for postmenopausal females

Or pre- or perimenopausal and amenable to being treated with the luteinizing hormone-releasing hormone (LHRH) agonist goserelin

Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 28 days prior to first dose of treatment. If patients have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial.

- Patients must not have received more than two prior lines of hormonal therapy in the locally advanced or metastatic setting. In addition, at least one line of treatment must be a CDK4/6i AND patients must have experienced disease recurrence or progression during or after CDK4/6i therapy, which must have been administered for a minimum of 8 weeks prior to progression.
- Patients for whom endocrine therapy (e.g., fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at the time of entry into the study, as per national or local treatment guidelines
- Women of childbearing potential (i.e., not postmenopausal for at least 12 months or surgically sterile) must have a negative serum pregnancy test result at screening, within 14 days prior to the first study drug administration
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods with a failure rate of < 1% per year during the treatment period and for *up to 2 years* after the last dose of study drug *(or based on the local prescribing information for fulvestrant).* Women must refrain from donating eggs during this same period.

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

  Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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

  A tumor biopsy sample (either archival or fresh) must be collected from all patients from either the primary tumor or a metastatic site (if clinically feasible) for determination of expression of BCL-2 by central laboratory testing for patient eligibility purposes and for exploratory research on biomarkers. The tumor specimen must contain adequate evaluable tumor cells (≥ 20% tumor cells) to enable BCL-2 IHC and other relevant biomarker analysis. Samples can be in a tissue block (preferred) or prepared as 20 unstained serial slides, and should be accompanied by an associated pathology report. If a tumor sample is not available, a fresh biopsy must be collected. The specimen must be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration samples are not acceptable.
- Have at least one measurable lesion via RECIST v1.1.

- Bone lesions that have been irradiated are not evaluable. Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.

- Have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0–1
- Have adequate organ and marrow function as defined below:
  - Hemoglobin ≥ 9 g/dL
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L
  - ALT and AST $\leq 2.5 \times$ upper limit of normal (ULN), with the following exception:
    - Patients with documented liver metastases: AST and/or ALT $\leq 5.0 \times$ ULN
  - Total serum bilirubin $\leq 1.5 \times$ ULN, with the following exception:
    - Patients with previously documented Gilbert syndrome who may have a bilirubin $< 5 \times$ ULN
  - Creatinine clearance ≥ 50 mL/min calculated with the use of the 24-hour creatinine clearance or modified Cockcroft-Gault equation (i.e., estimation of creatinine clearance rate [eCCr]) with the use of ideal body mass (IBM) instead of mass:

$$\text{eCCr} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ for female}]}{72 \times \text{serum creatinine (mg/dL)}}$$

    Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.04 \text{ for female}]}{\text{serum creatinine (μmol/L)}}$$

- Meet the following coagulation requirements:
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN within 14 days prior to initiation of study treatment
  - For patients receiving therapeutic anticoagulation:
    - INR or aPTT within therapeutic limits for at least 1 week immediately prior to initiation of study treatment
    - Stable anticoagulant regimen and stable INR during the 14 days immediately preceding initiation of study treatment
- Have a life expectancy > 3 months

Exclusion Criteria

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

- Prior treatment with fulvestrant or other selective estrogen receptor degraders (SERDs), venetoclax, or any investigational agent whose mechanism of action is to inhibit BCL-2
- Pregnant, lactating, or intending to become pregnant during the study
- Known untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control)

  Patients who have had previous treatment of brain metastases with surgery or radiotherapy may be eligible provided they meet all of the following criteria:
  - Evaluable or measurable disease per inclusion criteria outside the CNS is present
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No history of intracranial or spinal cord hemorrhage
  - Administration of treatment > 4 weeks prior to Cycle 1 Day 1 of the study
  - Asymptomatic from CNS metastases

- Recovered from significant (Grade ≥ 3) acute toxicity with no ongoing requirement for ≥ 10 mg of prednisone per day or an equivalent dose of other corticosteroids and no change in dose of corticosteroid for at least 2 weeks prior to Cycle 1 Day 1 of treatment

- Prior chemotherapy in the locally advanced or metastatic setting regardless of the duration of the treatment
- Any anti-cancer therapy received within 21 days of the first dose of study drug, including chemotherapy, radiotherapy, hormonal therapy, immunotherapy, antineoplastic vaccines, or other investigational therapy, with the following exception:
  - Radiotherapy with palliative intent to non-target sites is allowed
- Concurrent radiotherapy to any site or prior radiotherapy within 21 days of Cycle 1 Day 1 or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response) or prior radiotherapy to > 25% of bone marrow

  Prior radiation therapy is allowed if it was completed > 21 days before the Cycle 1 Day 1 treatment AND the patient has recovered from all toxicities to CTCAE Grade ≤ 1 AND disease evaluable for response outside of the radiation fields or evidence of post-radiation progression of previously irradiated sites of disease.
- Current severe, uncontrolled, systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic or infectious disease)
- Any major surgery within 28 days of the first dose of study drug or anticipation of the need for major surgery during the course of study treatment
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Steroid therapy for anti-neoplastic intent (stable steroid medication not more than 10 mg prednisolone per day or an equivalent dose of other corticosteroids for controlling CNS metastases is acceptable)
  - Strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin) or moderate CYP3A inhibitors (e.g., fluconazole, ciprofloxacin, verapamil)
  - Strong CYP3A inducers (e.g., carbamazepine, phenytoin) or moderate CYP3A inducers (e.g., efavirenz, modafinil)
- Consumption of one or more of the following within 3 days prior to the first dose of study drug:
  - Grapefruit or grapefruit products
  - Seville oranges including marmalade containing Seville oranges
  - Star fruit (carambola)
- Need for current chronic corticosteroid therapy (≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)
- Known infection with HIV or human T-cell leukemia virus 1
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Positive test results for hepatitis B core antibody (HBcAb) or hepatitis C virus (HCV) antibody at screening

  Patients who are positive for HCV antibody must be negative for HCV by polymerase chain reaction (PCR) to be eligible for study participation.

  Patients with a past or resolved hepatitis B virus (HBV) infection (defined as having a positive total HBcAb and negative hepatitis B surface antigen [HbsAg]) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.
- Active HCV infection, defined as having a positive HCV antibody test at screening

  Patients who have a positive HCV antibody test are eligible for the study if a PCR assay is negative for HCV RNA.

- History of other malignancies within the past 5 years except for treated skin basal cell carcinoma, squamous cell carcinoma, non-malignant melanoma $\leq$ 1.0 mm without ulceration, localized thyroid cancer, or cervical carcinoma in-situ
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study

  Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, or within 28 days following the last dose of venetoclax.
- Cardiopulmonary dysfunction as defined by any of the following prior to randomization:
  - History of NCI CTCAE v5.0 Grade $\geq$ 3 symptomatic congestive heart failure or New York Heart Association criteria Class $\geq$ II
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate $>$ 100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 [Mobitz 2] or third degree AV-block])
  - Significant symptoms (Grade $\geq$ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to randomization
  - Uncontrolled hypertension (systolic blood pressure $>$ 180 mmHg and/or diastolic blood pressure $>$ 100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
- Other medical or psychiatric conditions that, in the opinion of the investigatory, may interfere with the patient's participation in the study
- Inability or unwillingness to swallow pills or receive IM injections
- History of malabsorption syndrome or other condition that would interfere with enteral absorption
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Concurrent hormone replacement therapy
- Inability to comply with study and follow-up procedures
- Known hypersensitivity to any of the study medications (fulvestrant, venetoclax) or to any of the excipients

End of Study

The study duration will be the time from screening of the first patient through 2 years after the last patient is enrolled, or all patients in the study have withdrawn consent or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first.

Length of Study

With enrollment anticipated to last approximately 18 months, the total length of the study is expected to be approximately 43 months.

Investigational Medicinal Products

The investigational medicinal products (IMPs) used in this study are venetoclax and fulvestrant.

Test Product (Investigational Drug)

Venetoclax: Study patients will self-administer venetoclax tablets by mouth daily. Venetoclax is formulated as 100-mg tablets, so patients will take eight 100-mg tablets daily to receive an

800-mg dose. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the patient's first meal of the day (e.g., breakfast).

Comparator

Fulvestrant: Fulvestrant 500 mg will be administered in the clinic as two 250-mg IM injections on Cycle 1 Days 1 and 15 and then on Day 1 of each subsequent 28-day cycle.

Non-Investigational Medicinal Products

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. Granulocyte stimulating factor (G-CSF) will be administered for neutropenia as indicated. At the discretion of the investigator, a prophylactic oral agent (e.g., allopurinol 300 mg QD) may be initiated in patients who are deemed to be at the risk of tumor lysis syndrome (TLS) in order to reduce the uric acid level.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is clinical benefit, defined as complete response (CR), partial response (PR), or stable disease (SD) lasting $\geq$24 weeks from randomization in patients with measurable disease at baseline, as determined by the investigator according to RECIST v1.1. Patients with no response assessments for any reason will be considered non-responders.

The clinical benefit rate (CBR) analysis will be conducted for the intent-to-treat (ITT) population, the BCL-2 high subgroup, and the BCL-2 low subgroup. The confidence intervals for the difference in CBR between the two treatment arms will be determined using the normal approximation to the binomial distribution. An estimate of the CBR and its 95% CI will be calculated for each treatment arm.

Determination of Sample Size

Approximately 100 patients need to be recruited and randomized in a 1:1 ratio to two treatment arms (venetoclax + fulvestrant and fulvestrant). The study will enroll both BCL-2 high ($\geq$50% of tumor cells stained with an intensity of IHC 2+ or 3+) and low ($\geq$50% of tumor cells stained with an intensity of IHC 0 or 1^+ and $<$50% IHC 2^+ or 3^+) patients, and it is planned to enroll approximately 50 BCL-2-high patients.

The sample size of 100 patients provides precision of 15% for 80% CI when calculating the absolute difference in the CBR between the two arms assuming the expected observed CBR in the control arm is 40% and in the venetoclax arm is 60% (i.e., the 80% CI for difference in CBR is from 5% to 35%).

Interim Analyses

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AI	aromatase inhibitor
ALP	alkaline phosphatase
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AV	atrioventricular
BCL-2	B-cell lymphoma 2
BCRP	breast cancer resistance protein
BG	O_6-benzylguanine
BR	bendamustine+rituximab
BSA	body surface area
CAP	College of American Pathologists
CBR	clinical benefit rate
CDK4	cyclin-dependent kinase 4
CDK6	cyclin-dependent kinase 6
CLL	chronic lymphocytic leukemia
CR	complete response
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug–drug interaction
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
eCCr	estimation of creatinine clearance rate
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
ER+	estrogen receptor-positive
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded
G-CHOP	obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone
G-CSF	granulocyte stimulating factor
GHS	global health status

HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor
HIPAA	Health Insurance Portability and Accountability Act
HR+	hormone receptor-positive
HRQoL	health-related quality of life
IBM	ideal body mass
ICH	International Council for Harmonisation
IHC	immunohistochemistry
IM	intramuscular
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITT	intent-to-treat
IxRS	interactive voice or web-based response system
LHRH	luteinizing hormone–releasing hormone
MBC	metastatic breast cancer
MM	multiple myeloma
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NSG	NOD-SCID-ILR2γ_c -/-
OATP1B1	organic anion transporter protein 1B1
OR	objective response
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PO	orally
PR	partial response

PRO	patient-reported outcome
QD	once a day
QLQ-C30	Quality of Life Questionnaire–Core 30
QTc	QT interval corrected
QTcF	QT interval corrected through use of Fridericia's formula
R-CHOP	rituxan plus cyclophosphamide, doxorubicin, vincristine, and prednisone
RECIST	Response Evaluation Criteria in Solid Tumors
SC	subcutaneous
SD	stable disease
SERD	selective estrogen receptor degraders
SERMS	selective estrogen receptor modulators
SLL	small lymphocytic lymphoma
SOC	standard of care
TLS	tumor lysis syndrome
ULN	upper limit of normal
WTS	whole transcriptome sequencing

1. BACKGROUND

1.1 BACKGROUND ON ESTROGEN RECEPTOR-POSITIVE HER2-NEGATIVE ADVANCED OR METASTATIC BREAST CANCER

Breast cancer is the most frequent cancer diagnosed in women, with an estimated global incidence of 1.67 million new cases reported in 2012 (Ferlay et al. 2013). Breast cancer accounts for approximately 15% (approximately 522,000 cases) of all cancer deaths. Breast cancer mortality rates differ by geographical region, with more favorable survival rates in more developed regions of the world (Ferlay et al. 2013).

Estrogen receptor-positive (ER+)/human epidermal growth factor receptor (HER2)-negative breast cancer accounts for 60%–70% of all breast cancers. The standard-of-care (SOC) treatment for patients with ER+ breast cancer takes several factors into consideration including the stage of disease and recurrence score (Senkus et al. 2013; NCCN 2014). In the adjuvant treatment setting, endocrine therapy alone may be considered for patients with low volume disease (tumor size $\leq$0.5 cm, node-negative disease) and in patients with a low ($<$18) recurrence score using a 21-gene reverse transcriptase polymerase chain reaction (PCR) assay. Sequential treatment with chemotherapy followed by endocrine treatment should be considered for those patients with node-positive cancers or tumors $>$0.5 cm in size, and with intermediate (18–30) to high ($\leq$31) recurrence scores.

Administration of tamoxifen with consideration for ovarian ablation or suppression is recommended in premenopausal women (Senkus et al. 2013). The administration of aromatase inhibitors (AIs) as initial treatment or as a sequential treatment following tamoxifen has been recommended for postmenopausal women (Burstein et al. 2010; Senkus et al. 2013).

Endocrine treatment options in the treatment of postmenopausal women whose cancer has recurred after adjuvant therapy include nonsteroidal AIs (anastrozole, letrozole), steroidal AIs (exemestane), ER down-regulators (fulvestrant), and ER modulators (tamoxifen, toremifene). Meta-analyses suggest that AIs may be superior to tamoxifen in prolonging the time to disease progression in this treatment setting (Bonneterre et al. 2000; Nabholtz et al. 2000; Paridaens et al. 2008; Gibson et al. 2009). Treatment with fulvestrant may offer a survival advantage over anastrozole (Gibson et al. 2009). Very little evidence is available to support an optimal endocrine therapy sequence in the metastatic setting (NCCN 2014). The choice of agent, sequence of agents, and duration of treatment should be guided by practical considerations, such as prior endocrine treatment response and each agent's safety profile.

More recently, inhibitors specific for cyclin-dependent kinase 4 (CDK4) and cyclin-dependent kinase 6 (CDK6) have entered clinical practice for patients with ER+ breast cancer. Three selective cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) are now

approved: palbociclib, ribociclib, and abemaciclib. Positive results from several Phase II and III studies (PALOMA 1, 2, and 3 studies) have resulted in the U.S. Food and Drug Administration (FDA) and European Union approval of palbociclib, as first- or second-line treatment of hormone receptor-positive (HR+) breast cancer in combination with endocrine therapy. In the first-line setting of metastatic HR+ breast cancer, the combination of palbociclib with letrozole increased the median progression-free survival (PFS) and objective response rate (ORR) of letrozole therapy alone (PFS: 20.2 months vs. 10.3 months; ORR: 55.4% vs. 39.4%), providing a significant improvement in therapy options for patients with HR+ breast cancer. Based on the results of these trials, the 2016 American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology guidelines state that palbociclib in combination with endocrine therapy can be considered for treatment of HR+ metastatic breast cancer (MBC) in the first- or second-line setting (Rugo et al. 2016; Cardoso et al. 2017). Other CDK4/6i, such as ribociclib and abemaciclib, are approved by the FDA for the initial treatment of HR+ advanced or MBC, in combination with an AI for ribociclib and in combination with fulvestrant and in monotherapy for abemaciclib. However, despite these promising results, mechanisms of acquired resistance to CDK4/6i, as well as anecdotal evidence, suggest poor patient outcomes following CDK4/6i treatments and highlight the unmet medical need for identifying new therapeutic regimens for these patients.

Although endocrine therapy can provide prolonged disease control, recurrence and therapeutic resistance remains a significant problem for patients with HR+ advanced breast cancer. Patients who experience disease progression on endocrine therapies could range from patients with bone-only metastasis to those who have visceral crisis with multiple organ involvement. Our understanding of the mechanisms of resistance to endocrine therapy has improved in recent years. Mechanisms that can lead to primary and/or secondary hormonal resistance in ER+ breast cancer include a decrease or loss of ER expression or an upregulation of growth factor signalling pathways, such as the epidermal growth factor receptor or HER2. Recently, mutations in the gene that encodes ER (*ESR1*) have been identified in metastatic ER+ tumors and are associated with resistance to anti-estrogen therapies (Robinson et al. 2013; Toy et al. 2013; Jeselsohn et al. 2014). In addition to the enhanced understanding of endocrine resistance in ER+ breast cancer, significant efforts are underway to address the treatments for patients who develop this resistance. However, despite the development of new therapies, treatment of endocrine-resistant, HR+ breast cancer remains an area of high unmet need. Therefore, other markers, such as B-cell lymphoma 2 (BCL-2), are being investigated in order to develop treatments to fill this area of unmet medical need.

1.2 BCL-2 SIGNALING PATHWAY AND CANCER

Cancer cells are characterized by their capacity for relentless growth, survival, and evasion of cell death (Adams and Cory 2007; Strasser et al. 2011). Apoptosis is the dominant mode of programmed cell death with two distinct pathways: the intrinsic BCL-2 regulated mitochondrial pathway and the extrinsic death receptor pathway

(Strasser et al. 2011). BCL-2 is overexpressed in approximately 75% of breast cancer and has emerged as a prognostic marker (Dawson et al. 2010). This is demonstrated by the presence of BCL-2 protein as a component of Oncotype DX® a 21-gene recurrence score used to predict the risk of breast cancer recurrence in ER+, node-negative early stage disease (Paik et al. 2004).

BCL-2 has emerged as a promising therapeutic target in hematopoietic and possibly solid tumors. Patient derived xenograft tumor models of luminal B breast cancer demonstrated significantly improved tumor response and overall survival (OS) when treated with the BCL-2 inhibitor ABT-737 in combination with tamoxifen, compared with tamoxifen alone (Oakes et al. 2012; Vaillant et al. 2013). Similar efficacy was observed using the BCL-2 inhibitor venetoclax, suggesting that BCL-2 is a crucial target. To date, venetoclax has been studied in multiple early phase clinical trials in relapsed/refractory hematopoietic malignancies and recently in combination with tamoxifen for patients with ER+, BCL-2 positive MBC (Registration ACTRN12615000702516). This trial is still recruiting patients. An interim report of the dose-escalation phase of this trial was presented at ASCO in June 2016 and demonstrated the safety and efficacy for the combination of tamoxifen and venetoclax in ER+ MBC (Lindeman et al. 2017).

1.3 BACKGROUND ON VENETOCLAX

Venetoclax (also referred to as GDC-0199, RO5537382, ABT-199, A-1195425.0, Venclexta®, and Venclyxto®) is a novel, orally bioavailable, small-molecule BCL-2 family inhibitor in the biaryl acylsulfonamide chemical class.

Venetoclax has been extensively studied in oncology, particularly in hematological malignancies. Since 2011, multiple ongoing Phase I/II AbbVie and Phase I/II/III Genentech/Roche clinical studies are evaluating the safety, tolerability, pharmacokinetics, and efficacy of venetoclax as monotherapy or in combination with other therapies (e.g., rituximab, obinutuzumab, bendamustine+rituximab [BR], O_6-benzylguanine [BG], rituxan plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP], obinutuzumab plus CHOP [G-CHOP], bortezomib plus dexamethasone, azacitidine or decitabine, and cytarabine) in patients with hematologic malignancies (including chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL], non-Hodgkin lymphoma [NHL], multiple myeloma [MM], and acute myeloid leukemia [AML]). Data are available from drug-drug interaction (DDI) studies of venetoclax interaction with ketoconazole, with rifampin, and with warfarin. Additionally, two Phase III studies are ongoing: one study in relapsed/refractory CLL exploring the combination of venetoclax and rituximab against BR, and one Phase III study in first-line CLL exploring the combination of venetoclax and obinutuzumab against obinutuzumab plus chlorambucil.

Refer to the Venetoclax Investigator's Brochure for details on nonclinical and clinical studies.

The two-drug combination (i.e., venetoclax plus fulvestrant) proposed for the treatment of ER+ MBC has been evaluated in a nonclinical model for pharmacologic proof of concept. In addition, the data on the individual agents have been reviewed for potential DDI or overlapping toxicities. The results of this nonclinical study and data analysis are summarized as follows:

- In the 315T ER+ human breast cancer xenografts grown in NOD-SCID-ILR2γ_c-/- (NSG) mice, fulvestrant, administered subcutaneous (SC) once weekly, in combination with venetoclax, administered orally once a day (QD) for 5 days per week, for 3 weeks, enhanced tumor growth inhibition and significantly increased survival when compared with fulvestrant monotherapy. All drugs and the combination were tolerated based on no signs of moribundity during the treatment period.
- The combination of venetoclax and fulvestrant significantly increased survival in NSG mice bearing 315T xenografts when compared with fulvestrant alone (38 days vs. 25 days; $p < 0.005$).
- The nonclinical data demonstrate that the combination of venetoclax with fulvestrant is more efficacious than either agent alone in an ER+ patient-derived xenograft in vivo model and has low risk for off-target safety pharmacology effects.
- As venetoclax produced no CNS/neurological effects in non-clinical studies the risk for any significant overlapping CNS/neurological or cardiovascular effects is considered minimal.
- Based on the known safety profiles and pharmacokinetics, the potential for DDI with the venetoclax and fulvestrant combination is considered to be low.
- Both venetoclax and fulvestrant have the potential to cause reproductive organ and embryo-fetal developmental toxicities as single agents so there is the potential for this combination to cause overlapping or more/additional reproductive and embryo-fetal toxicities than the individual molecules. No other potential overlapping toxicities were identified from nonclinical studies.
- For this drug combination, the doses are based on human clinical trial data from the two approved drugs. The recommended human dose of venetoclax of 800 mg QD continuously is based on a Phase Ib clinical trial of venetoclax in combination with tamoxifen (Lindeman et al. 2017; venetoclax + tamoxifen in MBC) using that dose and schedule without employing a ramp-up. A dose of 800 mg venetoclax is currently being explored as a combination partner in the treatment of NHL and MM. In contrast to what has been observed in hematological cancers treated with venetoclax, tumor lysis syndrome (TLS) was not seen in the Phase Ib study, and a dose ramp-up phase is not being recommended.
- Fulvestrant is recommended to be administered using the approved human dose and schedule: 500 mg administered in the clinic (before administration of venetoclax) as two intramuscular (IM) injections of 250 mg each on Cycle 1 Days 1 and 15 and on Day 1 of each subsequent 28-day cycle. Based on the mechanism of action and the nonclinical and clinical data available to date, the safety profile of venetoclax is well described and the potential overlapping toxicities between

venetoclax and fulvestrant are thought to be of minor clinical significance and manageable.

1.4 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

This study will enroll patients with ER+, HER2-negative, inoperable, locally advanced or MBC who had disease progression following treatment for first- or second-line metastatic disease with endocrine therapy that contains CDK4/6i, such as palbociclib, but does not include fulvestrant. Although CDK4/6 inhibitors in combination with endocrine therapy have demonstrated an improvement in PFS in first- or second-line settings, the acquired resistance to CDK4/6 inhibitors, as well as anecdotal evidence, suggest poor patient outcomes following CDK4/6i therapy, highlighting the need for identifying new therapeutic regimens for these patients.

Given this unmet clinical need for patients with endocrine-resistant disease and observed emergence of acquired resistance to CDK4/6i (O'Leary et al. 2016), this population is considered appropriate for trials of novel therapeutic candidates to identify effective post-CDK4/6i treatment regimens, including BCL-2 inhibitors.

At the primary analysis (clinical cut-off date of 5 August 2020, data read-out available on 29 September 2020), the efficacy and safety data from 103 patients enrolled in this study (intent-to-treat [ITT] population) was reported. A summary of findings from the primary analysis is provided below:

The study did not demonstrate a numerical improvement in the primary endpoint of clinical benefit rate (CBR) or the secondary endpoint of PFS in the venetoclax plus fulvestrant arm compared with the fulvestrant arm. The secondary endpoint of OS was not mature (27.2% event/patient ratio) with a median duration of survival follow-up of 9.89 months. The stratified hazard ratio was 2.56 (95% CI: 1.11 to 5.89).

Safety of the venetoclax plus fulvestrant was consistent with the known safety profile of the individual medicines. No new safety signals were identified. However, a higher proportion of deaths was observed in the venetoclax plus fulvestrant arm compared with the fulvestrant arm. In the ITT population, a total of 19 deaths (37.3%) was reported in the venetoclax plus fulvestrant arm compared with 9 deaths (17.3%) in the fulvestrant arm.

Deaths that occurred ≤28 days after the last dose of study drug were reported in 2 patients in the venetoclax plus fulvestrant arm (primary cause of death included 1 case due to adverse event and 1 case due to disease progression), compared with none in the fulvestrant arm. Deaths that occurred >28 days after the last dose of study drug were reported in 17 patients in the venetoclax plus fulvestrant arm (primary cause of death included 16 cases due to progressive disease, and 1 case related to other causes which was reported post-study), compared with 9 patients in the fulvestrant arm (primary cause of death included 8 cases due to progressive disease and 1 case due to pneumonia).

Overall, the results from the primary analysis do not support a positive benefit/risk profile for the treatment of venetoclax plus fulvestrant in patients with ER+, HER2-negative locally advanced or MBC who experienced disease recurrence or progression during or after CDK4/6 inhibitor therapy. While the Sponsor is carrying out additional analyses to further understand these results, it is no longer considered appropriate for patients in this study to receive venetoclax.

Investigators were informed on 8 October 2020, and as of this date, all active patients in the venetoclax plus fulvestrant arm of the study will be requested to discontinue the venetoclax treatment immediately, and will be given the option to continue fulvestrant treatment alone.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy of venetoclax (GDC-0199; ABT199) in combination with fulvestrant compared with fulvestrant alone in women with ER+, HER2-negative, locally advanced breast cancer not amenable to surgical or local therapy with curative intent or with MBC who experienced disease recurrence or progression during or after being treated with CDK4/6i therapy for at least 8 weeks prior to progression. Specific objectives and corresponding endpoints for the study are outlined in Table 1.

Table 1 Objectives and Corresponding Endpoints

Objectives	Corresponding Endpoints
Primary Efficacy Objective:	
• To evaluate the efficacy of venetoclax in combination with fulvestrant compared with fulvestrant alone	• Clinical benefit defined as CR, PR, or SD lasting ≥24 weeks from randomization in patients with measurable disease at baseline, as determined by the investigator according to RECIST v1.1.
Secondary Efficacy Objective:	
• To evaluate the efficacy of venetoclax in combination with fulvestrant compared with fulvestrant alone	• PFS, defined as the time from randomization to the first occurrence of disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first • Objective response, defined as CR or PR, as determined by the investigator according to RECIST v1.1 • DOR, defined as time from the first occurrence of a documented objective response to the time of the first documented disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first • OS, defined as the time from randomization to death from any cause
Safety Objective:	
• To evaluate safety and tolerability of venetoclax in combination with fulvestrant compared with fulvestrant alone	• To evaluate safety and tolerability of venetoclax in combination with fulvestrant compared with fulvestrant alone
Pharmacokinetic Objectives:	
• To assess the pharmacokinetics of venetoclax and fulvestrant following administration of venetoclax in combination with fulvestrant	• Plasma concentrations of venetoclax and fulvestrant at specified timepoints
• To assess potential drug-drug interactions between venetoclax and fulvestrant	• Plasma concentrations or PK parameters of venetoclax and fulvestrant given in combination compared with these agents given alone (based on historical data)
Biomarker Objectives:	
• To evaluate predictive, prognostic, and pharmacodynamic biomarkers in tumor tissue and plasma associated with disease activity, response to treatment, or resistance to venetoclax in combination with fulvestrant	• Baseline BCL-2 protein levels as measured by IHC correlating with clinical response measures • Expanded biomarkers (see Table 2) measured at baseline, on-treatment, and at end of treatment relative to clinical response measures

Objectives	Corresponding Endpoints
PRO Objectives:	
• To evaluate PROs of function, disease/treatment-related symptoms, and GHS/overall HRQoL associated with venetoclax in combination with fulvestrant compared with fulvestrant alone • To evaluate and compare PROs of disease-related pain in venetoclax in combination with fulvestrant compared with fulvestrant alone	• Mean and mean changes from baseline scores in functional (i.e., role, physical, emotional, and social), disease/treatment-related symptoms, and GHS/HRQoL by cycle as assessed by the scales (Questions 29 and 30) of the EORTC QLQ-C30 • Change in baseline pain score as assessed by the pain scale (Questions 9 and 19) of EORTC QLQ-C30

AEs = adverse events; AESI = adverse events of special interest; BCL-2=B-cell lymphoma 2; CR = complete response; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; GHS = global health status; HRQoL = health-related quality of life; IHC=immunohistochemistry; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire Core 30; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1; SAEs = serious adverse events; SD = stable disease.

Table 2 Biomarkers for Exploratory Research

Proposed Biomarkers	Sample Type	Timing
ctDNA	Plasma	Pre-dose at baseline and subsequent time points during treatment (see Appendix 1)
• Expression of BCL-2 and other markers of breast disease biology (i.e., ER, PR, HER2, Ki67, and other BCL-2 family members) • Mutations in cancer-related genes assessed by NGS of DNA • Expression of cancer-related genes assessed by quantification of RNA	Tumor tissue	Screening (mandatory) and (optional) at Cycle 3 Day 1 (±3 days) and at time of progression

BCL-2=B-cell lymphoma 2; ctDNA=circulating tumor DNA; ER=estrogen receptor; NGS=next-generation sequencing; PR=progesterone receptors.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a Phase II, multicenter, open-label, randomized study to compare the efficacy of venetoclax in combination with fulvestrant compared with fulvestrant alone in women with ER+, HER2-negative, inoperable, locally advanced or MBC who experienced disease recurrence or progression during or after treatment with CDK4/6i therapy for at

least 8 weeks. Approximately 100 patients from approximately 40 centers globally will be enrolled. Fresh tumor tissue (or archival tissue) will be collected during screening from all patients to confirm and determine HER2, ER, and BCL-2 status. ER status will be defined by using immunohistochemistry (IHC) per the ASCO/College of American Pathologists (CAP) criteria (Hammond et al. 2010), and HER2 negativity will be defined per the ASCO/CAP criteria (Wolff et al. 2013). BCL-2 expression will be assessed by a central laboratory using the Ventana BCL-2 IHC assay. BCL-2 high is defined as $\geq 50\%$ of tumor cells stained with an intensity of IHC 2^+ or 3^+, and BCL-2 low is defined as $\geq 50\%$ stained with an intensity of IHC 0 or 1^+ and $< 50\%$ stained an intensity of IHC 2^+ or 3^+.

Patients who do not initially meet all eligibility criteria may be rescreened once within 2 weeks, given that the reason for screening failure was not ER or HER-2 status (see Section 4.5.1 for further information).

Central laboratory assessments will occur prior to randomization. Patients must have measurable disease (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1]) locally advanced or metastatic disease with at least one evaluable lesion. Detailed information is listed in the inclusion and exclusion criteria in Section 4.1 and Appendix 4. Locally advanced disease must not be amenable to resection or other local therapy with curative intent.

Patients will be randomized in a 1:1 ratio to receive venetoclax in combination with fulvestrant or fulvestrant alone. Randomization will be stratified between the two arms on the basis of BCL-2 status and one versus two lines of prior therapy in the locally advanced/metastatic setting.

- **Venetoclax arm:** venetoclax 800-mg tablet (8×100-mg tablet formulation) taken orally (PO) QD beginning on Cycle 1 Day 1 and fulvestrant 500 mg administered as two 250-mg IM injections on Cycle 1 Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle.
- **Control arm:** fulvestrant 500 mg administered as two 250-mg IM injections on Cycle 1 Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle. No crossover to the venetoclax arm is permitted.

Tumor assessments will be conducted for all patients at screening and at every 8 weeks (± 5 days) from the date of randomization until Week 24 (± 5 days) and every 12 weeks (± 5 days) thereafter. Tumor assessments will be conducted regardless of dose delays or early discontinuation, until investigator-assessed disease progression (as specified below), the predefined end of the study (Section 3.3), or until death, whichever occurs first.

Study treatment for each patient will continue until disease progression, unacceptable toxicity, withdrawal of consent, death, or study termination by the Sponsor, whichever occurs first.

Diagnosis of disease progression should be supported by radiology assessments as per RECIST v1.1. All patients who are discontinued from all study treatment will return for a study drug discontinuation visit 28 days (+3 days) after the last dose of study treatment.

Patients who are discontinued from study treatment for reasons other than disease progression and have started follow-on treatment will be followed for survival approximately every *3 months, or more frequently,* until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are discontinued from study treatment for reasons other than disease progression and have not started follow-on treatment will be followed for disease status every 8 weeks (±5 days) from the date of randomization until Week 24 (±5 days) and then every 12 weeks (±5 days) thereafter until disease progression, death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

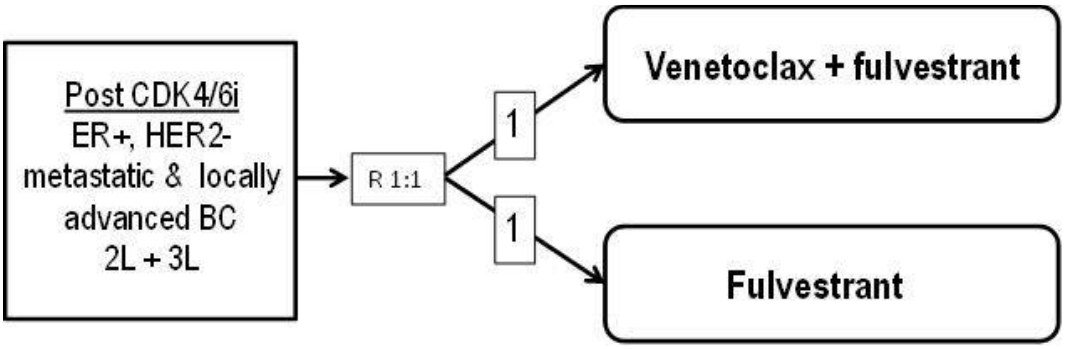
After disease progression, patients will be followed for survival and subsequent anti-cancer therapies approximately every *3 months, or more frequently,* until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Safety will be evaluated by monitoring the overall safety events, including all adverse events identified through physical examinations, and assessments of vital signs and laboratory test results. Such events will be graded by the investigators with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). Safety assessments from laboratory test results will include monitoring of hematology and blood chemistry.

As of 8 October 2020, all active patients in the venetoclax plus fulvestrant arm of the study will be requested to discontinue the venetoclax treatment immediately, and will be given the option to continue fulvestrant treatment alone.

The study schema is presented in Figure 1. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



2L = second line; 3L = third line; BC = breast cancer; BCL-2 = B-cell lymphoma 2; CDK4/6i = cyclin-dependent kinase 4/6 inhibitor; ER+ = estrogen receptor–positive; HER2– = human epidermal growth factor receptor–negative; R = randomization.
Note: Stratification is by one vs. two lines of prior therapy in the locally advanced/metastatic setting and BCL-2 High vs. Low (see Section 4.2).

3.2 INTERNAL MONITORING COMMITTEE

An Internal Monitoring Committee (IMC) will monitor the totality of the safety data collected during the clinical trial. The IMC will convene to review initial safety data after 5 patients in each arm (10 patients) have been randomized and treated for at least one cycle or 3 months after the first patient has been enrolled, whichever comes first. Thereafter, the IMC will convene approximately every 6 months, or more frequently as needed, to review cumulative safety data, including data regarding serious adverse events, death, events Grade ≥3, clinically significant laboratory abnormalities, and adverse events of special interest.

The IMC will include at a minimum the study Medical Monitor, a safety scientist, biostatistician, and a designated Sponsor medical oncologist who is not the Medical Monitor and is not associated with the study. Representatives from other Sponsor function areas may be included as ad hoc members. The IMC will operate according to a pre-specified charter that will outline the IMC members, roles, responsibilities, and communication processes, and this charter will be made available upon request to the appropriate regulatory agencies.

3.3 END OF STUDY AND LENGTH OF STUDY

The study duration will be the time from screening of the first patient through 2 years after the last patient is enrolled, or all patients in the study have withdrawn consent or died, or if the study is prematurely terminated by the Sponsor, whichever occurs first. With enrollment anticipated to last approximately 18 months, the total length of the study is expected to be approximately 43 months.

3.4 RATIONALE FOR STUDY DESIGN

3.4.1 Rationale for Venetoclax Dose and Schedule

Venetoclax has been investigated in multiple trials of hematopoietic malignancies at doses ranging from 200 mg to 1200 mg, as monotherapy and in combination with other agents including dexamethasone, rituximab, obinutuzumab, bortezomib, and chemotherapy. The safety, tolerability, and efficacy of venetoclax have been confirmed. Venetoclax was granted approval in the United States (see Venclexta™ U.S. Prescribing Information 2016) and conditional market approval by the European Medicines Agency (EMA) (Venclyxto® EMA Summary of Product Characteristics 2016) as monotherapy for the treatment of patients with CLL who have 17p deletion at the dose of 400 mg QD.
A Phase I dose-escalation trial investigating combinations of various doses of venetoclax (including 200 mg, 400 mg, 600 mg, and 800 mg) with tamoxifen assessed the safety and tolerability of venetoclax in combination with tamoxifen in patients with ER+, BCL-2–positive MBC. Although dose-limiting toxicity (DLT) was not reached, venetoclax at the dose of 800 mg QD orally was demonstrated to be safe and tolerable in combination with tamoxifen. The nature and frequencies of these adverse events were consistent with the known safety profiles of venetoclax and tamoxifen, and no Grade 5 adverse events or DLTs occurred during the DLT observation period, based on the preliminary evidence of clinically relevant activity of venetoclax during the dose-escalation phase (Lindeman et al. 2017). Therefore, the 800-mg dose was selected for the expansion phase of the study (venetoclax + tamoxifen), which is ongoing and planned to enroll approximately 30 patients with ER+ metastatic breast cancer. Additionally, as the overlapping toxicities and potential for DDI between venetoclax and fulvestrant are thought to be of minimum significance, there is no dose adjustment considered for the combination of these two products.

3.4.2 Rationale for Patient Population

HR+ breast cancer accounts for over 70% of breast cancer subtypes. Until the recent emergence of selective CDK4/6 inhibitors, endocrine therapy remained the SOC treatment for metastatic disease through multiple lines of therapy followed by chemotherapy in the late metastatic, endocrine therapy-resistant setting. Recent data from the PALOMA 3 trial has demonstrated the efficacy of combined palbociclib and fulvestrant in premenopausal patients who were treated with goserelin as well as those with postmenopausal status (Loibl et al. 2017). However, despite recent PFS improvements with CDK4/6i, the emergence of acquired resistance to CDK4/6i highlights the continued unmet need to identify new treatment regimens for patients with second-line metastatic ER+ breast cancer following such treatment (O'Leary et al. 2016). Despite the benefits from current endocrine therapies and chemotherapies, HR+ MBC remains an incurable disease and the majority of patients will eventually progress and subsequently die from the disease. BCL-2 is expressed in approximately 75% of breast cancer (Callagy et al. 2006; Dawson et al. 2010) and is an established therapeutic target in CLL. Early phase clinical trials have demonstrated efficacy using the BCL-2 inhibitor venetoclax in combination with tamoxifen for patients with ER+ positive, BCL-2 positive

MBC, providing a rationale for investigating BCL-2 inhibitor treatment regimens in this patient population.

3.4.3 Rationale for Control Treatment

Treatment for HR+, HER2-negative breast cancer usually consists of multiple rounds of endocrine therapy with or without selective CDK4/6 inhibitors followed by cytotoxic chemotherapy once all endocrine therapy options have been exhausted or symptomatic or rapid disease progression warrants the use of cytotoxic chemotherapy. Fulvestrant has been approved by the FDA and EMA for the treatment of HR+ or ER+, locally advanced or MBC in postmenopausal women with disease progression following prior anti-estrogen therapy (Howell et al. 2002; Osborne et al. 2002; Di Leo et al. 2010) and postmenopausal women not previously treated with endocrine therapy. Fulvestrant is not indicated for use in the adjuvant setting, whereas AIs are currently approved for use and are considered the SOC (in the United States and European Union) in this setting. Therefore, given the unique mechanism of action and the current treatment paradigm that indicates the sequential use of endocrine therapies for patients without visceral crisis (Senkus et al. 2013) for treatment of locally recurrent or MBC, fulvestrant represents an appropriate treatment option for patients whose disease failed to respond to prior AI therapy.

3.4.4 Rationale for Biomarker Assessments

Breast cancer is a heterogeneous disease that can be divided into at least four distinct molecular subtypes defined as basal/triple-negative, HER2-enriched, and luminal subtypes A and B. Luminal breast cancers are characterized by elevated hormone receptor expression (Perou et al. 2000), and BCL-2 expression is enriched in these ER+ luminal subgroups (Vaillant et al. 2013). ER, progesterone receptor, and HER2 expression measures are used clinically to both establish prognosis as well as identify targeted treatment options.

While nonclinical studies have not shown single-agent activity by BCL-2 inhibitors in breast cancer, it has been demonstrated that ER inhibitors, such as tamoxifen, are more effective when used in combination with BCL-2 inhibitors (Vaillant et al. 2013). This observation suggests the potential for enhancement of anti-estrogen therapy in combination with anti-BCL-2 therapy. Molecules have been designed with different mechanisms to block activity driven by the ER, such as selective ER modulators (SERMS), steroidal and non-steroidal AIs, and estrogen-targeting therapies, such as fulvestrant (a selective ER degrader [SERD]), that compromise ER-driven signaling by degrading the receptor. SERDs are often applied when SERMs or AIs are no longer effective and are used in the MBC setting. Activity of SERDs, such as fulvestrant, may be enhanced by BCL-2 inhibition as, in addition to the fulvestrant-dependent reduction of ER driven BCL-2 expression; BCL-2 inhibitors, such as venetoclax, may block any residual BCL-2 activity that contributes to pathogenesis. As nonclinical studies have shown that BCL-2 protein levels may be predictive of response to venetoclax in

hematologic malignancies (Souers et al. 2013), there is potential for biological target-based (both ER and BCL-2) inhibition in MBC.

Even within luminal, ER+ breast cancer patients in whom BCL-2 expression is elevated relative to the other molecular subtypes, BCL-2 levels can vary. Currently, there are limited data about the correlation of response to BCL-2 inhibition in breast cancer and BCL-2 expression levels. BCL-2 levels are elevated in estrogen-positive subgroups relative to the other molecular subgroups that comprise breast cancer. Therefore, predictive biomarker samples collected prior to dosing will be assessed in an effort to identify those patients with BCL-2–driven pathogenesis who are most likely to respond to venetoclax. The study aims to prospectively explore if BCL-2 expression might have predictive or prognostic value or might be associated with disease progression in the studied population.

Fresh tissue acquisition in some patients with MBC may not be feasible; consequently, assessment of more easily accessible biomarkers in circulation is of high interest. In addition to identification of disease-specific, potentially prognostic, or predictive biomarkers in predose, baseline blood specimens, on-treatment collection of blood to evaluate circulating tumor DNA (ctDNA) may enable identification of biomarkers informing the relationship with established clinical response assessments, the monitoring of disease progression, and the identification of markers of resistance.

Tumor tissue samples will be analyzed through use of IHC to assess protein expression, whole transcriptome sequencing (WTS), and/or RNA sequencing to assess gene expression levels. Both tissue and blood samples will be analyzed by next-generation sequencing (NGS) to identify somatic mutations that are predictive of response to study drug, are associated with progression, are associated with acquired resistance to study drug, or can increase the knowledge and understanding of disease biology.

3.4.5 Rationale for Stratification by B-Cell Lymphoma-2 Status

BCL-2 levels are elevated in estrogen positive tumors; however, currently there is little data demonstrating a pathogenic role for BCL-2 in breast cancer. Venetoclax specifically inhibits BCL-2 activity, and there is potential that BCL-2 target-expression levels may correlate with activity. The role of BCL-2 in pathogenesis is confounded by the prognostic profile associated with the estrogen-positive subtype. In order to distinguish the potential for predictive value of BCL-2 expression levels with targeted BCL-2 inhibition, patients will not only be randomized into fulvestrant and venetoclax versus fulvestrant alone arms to distinguish prognostic effects but also stratified into BCL-2 high ($\geq$ 50% of tumor cells stained with an intensity of IHC 2^+ or 3^+) and BCL-2 low ($\geq$ 50% stained with an intensity of IHC 0 or 1^+ and $<$ 50% stained an intensity of IHC 2^+ or 3^+) populations. In nonclinical analyses, elevated BCL-2 expression levels in NHL cell lines correlate with venetoclax activity using this high versus low cutoff. Stratification will enable evaluation of the correlation between BCL-2 expression and venetoclax activity in breast cancer. Responses will be evaluated by comparing the two stratified subgroups.

Since a cutoff for BCL-2 levels in breast cancer has not been established, retrospective analyses may also be performed to evaluate alternative cutoffs.

3.4.6 Rationale for Patient-Reported Outcome Assessments

As MBC is not curable with currently approved and available therapies, the main goals of treatment are to prolong survival and maintain or improve quality of life (Cardoso et al. 2012). Disease symptoms are dependent on sites of metastases (Irvin et al. 2011), and patients can have bone involvement. Examining and measuring patients' pain, their global health status (GHS)/overall health-related quality of life (HRQoL), as well as their treatment-related symptoms and their interference with daily life is important and will be assessed using validated PRO assessments.

The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) will be administered to patients to assess disease/treatment-related symptoms, functioning, and HRQoL (see Section 4.5.9 and Appendix 5).

In addition, for patients with metastatic disease, pain can be a serious symptom. Therefore, measuring pain and the progression of pain and its impact on patients are important; thus, this symptom will be assessed using the pain scale from the EORTC QLQ-C30.

The EORTC QLQ-C30 will be assessed at baseline (Cycle 1, Day 1), at Day 1 of each subsequent cycle, and at the treatment discontinuation visit (see Appendix 1). The PRO data will be collected using paper questionnaires completed at the clinic site visit.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 100 patients with ER+, HER2-negative locally advanced or MBC will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Female and ≥ 18 years of age at time of signing Informed Consent Form
- Signed Informed Consent Form
- Histological or cytological confirmation of ER+ invasive carcinoma of the breast with the following tumor molecular characteristics:
  - Documented ER+ defined by using IHC per ASCO/CAP criteria (Hammond et al. 2010)
  - Documented HER2-negative per ASCO/CAP criteria (Wolff et al. 2013). Patients who were originally diagnosed with HER2-positive breast cancer that converted to HER2-negative MBC are NOT eligible to take part in this study.

- Evaluable sample for BCL-2 IHC value at the time of screening

- Evidence of metastatic or locally advanced disease not amenable to surgical or local therapy with curative intent
- Be either:

  Postmenopausal, defined as:

  - Age ≥60 years OR,
  - Age <60 years AND have undergone bilateral oophorectomy, medically confirmed ovarian failure OR,
  - Age <60 years AND have had cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have serum levels of estradiol and follicle-stimulating hormone within the laboratory's reference range for postmenopausal females

  Or pre- or perimenopausal and amenable to being treated with the luteinizing hormone-releasing hormone (LHRH) agonist goserelin

  Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 28 days prior to first dose of treatment. If patients have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial.
- Patients must not have received more than two prior lines of hormonal therapy in the locally advanced or metastatic setting. In addition, at least one line of treatment must be a CDK4/6i AND patients must have experienced disease recurrence or progression during or after CDK4/6i therapy, which must have been administered for a minimum of 8 weeks prior to progression.
- Patients for whom endocrine therapy (e.g., fulvestrant) is recommended and treatment with cytotoxic chemotherapy is not indicated at the time of entry into the study, as per national or local treatment guidelines.
- Women of childbearing potential (i.e., not postmenopausal for at least 12 months or surgically sterile) must have a negative serum pregnancy test result at screening, within 14 days prior to the first study drug administration
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use non-hormonal contraceptive methods with a failure rate of <1% per year during the treatment period and for *up to 2 years* after the last dose of study drug *(or based on the local prescribing information for fulvestrant).* Women must refrain from donating eggs during this same period.

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

  Examples of non-hormonal contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, and copper intrauterine devices.

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

- Willing to provide tumor biopsy sample

  A tumor biopsy sample (either archival or fresh) must be collected from all patients from either the primary tumor or a metastatic site (if clinically feasible) for determination of expression of BCL-2 by central laboratory testing for patient eligibility purposes and for exploratory research on biomarkers. The tumor specimen must contain adequate evaluable tumor cells (≥ 20% tumor cells) to enable BCL-2 IHC and other relevant biomarker analysis. Samples can be in a tissue block (preferred) or prepared as 20 unstained serial slides, and should be accompanied by an associated pathology report. If a tumor sample is not available, a fresh biopsy must be collected. The specimen must be a formalin-fixed, paraffin-embedded (FFPE) tumor specimen, or another appropriate fixative must be used (notation of the type of fixative should be included). Cytological or fine-needle aspiration samples are not acceptable.

- Have at least one measurable lesion via RECIST v1.1.
  - Bone lesions that have been irradiated are not evaluable. Previously irradiated lesions can be considered as measurable disease only if progressive disease has been unequivocally documented at that site since radiation.
- Have an Eastern Cooperative Oncology Group (ECOG) Performance Score of 0–1
- Have adequate organ and marrow function as defined below:
  - Hemoglobin ≥ 9 g/dL
  - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
  - Platelet count $\geq 100 \times 10^9$/L
  - ALT and AST $\leq 2.5 \times$ upper limit of normal (ULN), with the following exception:
    - Patients with documented liver metastases: AST and/or ALT $\leq 5.0 \times$ ULN
  - Total serum bilirubin $\leq 1.5 \times$ ULN, with the following exception:
    - Patients with previously documented Gilbert syndrome who may have a bilirubin $< 5 \times$ ULN
  - Creatinine clearance ≥ 50 mL/min calculated with the use of the 24-hour creatinine clearance or modified Cockcroft-Gault equation (i.e., estimation of creatinine clearance rate [eCCr]) with the use of ideal body mass (IBM) instead of mass):

$$\text{eCCr} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ for female}]}{72 \times \text{serum creatinine (mg/dL)}}$$

Or, if serum creatinine is in μmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.04 \text{ for female}]}{\text{serum creatinine (μmol/L)}}$$

- Meet the following coagulation requirements:
  - For patients not receiving therapeutic anticoagulation: INR or aPTT $\leq 1.5 \times$ ULN within 14 days prior to initiation of study treatment
  - For patients receiving therapeutic anticoagulation:
    - INR or aPTT within therapeutic limits for at least 1 week immediately prior to initiation of study treatment
    - Stable anticoagulant regimen and stable INR during the 14 days immediately preceding initiation of study treatment
- Have a life expectancy $>$ 3 months

4.1.2 Exclusion Criteria

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

- Prior treatment with fulvestrant or other SERDs, venetoclax, or any investigational agent whose mechanism of action is to inhibit BCL-2
- Pregnant, lactating, or intending to become pregnant during the study
- Known untreated or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control)

  Patients who have had previous treatment of brain metastases with surgery or radiotherapy may be eligible provided they meet all of the following criteria:
  - Evaluable or measurable disease per inclusion criteria outside the CNS is present
  - Radiographic demonstration of improvement upon the completion of CNS-directed therapy and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No history of intracranial or spinal cord hemorrhage
  - Administration of treatment $>$ 4 weeks prior to Cycle 1 Day 1 of the study
  - Asymptomatic from CNS metastases
  - Recovered from significant (Grade $\geq$ 3) acute toxicity with no ongoing requirement for $\geq$ 10 mg of prednisone per day or an equivalent dose of other corticosteroids and no change in dose of corticosteroid for at least 2 weeks prior to Cycle 1 Day 1 of treatment
- Prior chemotherapy in the locally advanced or metastatic setting regardless of the duration of the treatment
- Any anti-cancer therapy received within 21 days of the first dose of study drug, including chemotherapy, radiotherapy, hormonal therapy, immunotherapy, antineoplastic vaccines, or other investigational therapy, with the following exception:
  - Radiotherapy with palliative intent to non-target sites is allowed

- Concurrent radiotherapy to any site or prior radiotherapy within 21 days of Cycle 1 Day 1 or previous radiotherapy to the target lesion sites (the sites that are to be followed for determination of a response) or prior radiotherapy to >25% of bone marrow

  Prior radiation therapy is allowed if it was completed >21 days before the Cycle 1 Day 1 treatment AND the patient has recovered from all toxicities to CTCAE Grade ≤1 AND disease evaluable for response outside of the radiation fields or evidence of post-radiation progression of previously irradiated sites of disease.
- Current severe, uncontrolled, systemic disease (e.g., clinically significant cardiovascular, pulmonary, metabolic or infectious disease)
- Any major surgery within 28 days of the first dose of study drug or anticipation of the need for major surgery during the course of study treatment
- Administration of the following agents within 7 days prior to the first dose of study drug:
  - Steroid therapy for anti-neoplastic intent (stable steroid medication not more than 10 mg prednisolone per day or an equivalent dose of other corticosteroids for controlling CNS metastases is acceptable)
  - Strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin) or moderate CYP3A inhibitors (e.g., fluconazole, ciprofloxacin, verapamil) (see Appendix 3)
  - Strong CYP3A inducers (e.g., carbamazepine, phenytoin) or moderate CYP3A inducers (e.g., efavirenz, modafinil) (see Appendix 3)
- Consumption of one or more of the following within 3 days prior to the first dose of study drug:
  - Grapefruit or grapefruit products
  - Seville oranges including marmalade containing Seville oranges
  - Star fruit (carambola)
- Need for current chronic corticosteroid therapy (≥10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids)
- Known infection with HIV or human T-cell leukemia virus 1
- Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) within 4 weeks prior to Cycle 1 Day 1
- Positive test results for hepatitis B core antibody (HBcAb) or hepatitis C virus (HCV) antibody at screening

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

  Patients with a past or resolved hepatitis B virus (HBV) infection (defined as having a positive total HBcAb and negative hepatitis B surface antigen [HbsAg])

may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.

- Active HCV infection, defined as having a positive HCV antibody test at screening

  Patients who have a positive HCV antibody test are eligible for the study if a PCR assay is negative for HCV RNA.

- History of other malignancies within the past 5 years except for treated skin basal cell carcinoma, squamous cell carcinoma, non-malignant melanoma ≤ 1.0 mm without ulceration, localized thyroid cancer, or cervical carcinoma in-situ
- Administration of a live, attenuated vaccine within 4 weeks prior to initiation of study treatment or anticipation of need for such a vaccine during the study

  Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to randomization, during treatment, or within 28 days following the last dose of venetoclax.

- Cardiopulmonary dysfunction as defined by any of the following prior to randomization:
  - History of NCI CTCAE v5.0 Grade ≥ 3 symptomatic congestive heart failure or New York Heart Association criteria Class $\geq$ II
  - Angina pectoris requiring anti-anginal medication, serious cardiac arrhythmia not controlled by adequate medication, severe conduction abnormality, or clinically significant valvular disease
  - High-risk uncontrolled arrhythmias (i.e., atrial tachycardia with a heart rate >100/min at rest, significant ventricular arrhythmia [ventricular tachycardia], or higher-grade atrioventricular [AV]-block [second-degree AV-block Type 2 {Mobitz 2} or third degree AV-block])
  - Significant symptoms (Grade ≥ 2) relating to left ventricular dysfunction, cardiac arrhythmia, or cardiac ischemia
  - Myocardial infarction within 12 months prior to randomization
  - Uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg)
  - Evidence of transmural infarction on ECG
  - Requirement for oxygen therapy
- Other medical or psychiatric conditions that, in the opinion of the investigatory, may interfere with the patient's participation in the study
- Inability or unwillingness to swallow pills or receive IM injections
- History of malabsorption syndrome or other condition that would interfere with enteral absorption
- History of inflammatory bowel disease (e.g., Crohn's disease or ulcerative colitis) or active bowel inflammation (e.g., diverticulitis)
- Concurrent hormone replacement therapy

- Inability to comply with study and follow-up procedures
- Known hypersensitivity to any of the study medications (fulvestrant, venetoclax) or to any of the excipients

4.2 METHOD OF TREATMENT ASSIGNMENT

After written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established, the study site will enter demographic and baseline characteristics in the interactive voice or web-based response system (IxRS). For those patients who are eligible for enrollment, the study site will obtain the patient's identification number and treatment assignment from the IxRS.

Randomization will be conducted using a permuted block randomization method through the IxRS. Patients will be randomized into one of the two treatment arms in a 1:1 ratio based on the following stratification factors:

- BCL-2 status: high (≥ 50% IHC 2+ or 3+) versus low (≥ 50% IHC 0 or 1+ and < 50% IHC 2^+ or 3^+). It is planned to enroll approximately 50 BCL-2–high patients.
- Number of prior therapy in the locally advanced/metastatic setting: one versus two

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) used in this study are venetoclax and fulvestrant.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Venetoclax

Venetoclax will be supplied by the Sponsor. For information on the formulation, packaging, and handling of venetoclax, please see the Venetoclax Investigator's Brochure.

4.3.1.2 Fulvestrant

Fulvestrant will be supplied by the Sponsor in all participating countries, except the countries where procurement will be reimbursed. For countries in which the Sponsor is supplying fulvestrant, it will be supplied in sterile, single-patient, prefilled syringes containing 50 mg/mL fulvestrant as a 5-mL injection. For information on the formulation and handling of fulvestrant, please see the package insert.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Any overdose or incorrect administration of venetoclax or fulvestrant should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of any of the study treatments

should be recorded on the Adverse Event eCRF. Section 5.3.5.12 summarizes available safety data related to overdosing of venetoclax.

Guidelines for dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.3.

4.3.2.1 Venetoclax

Study patients will self-administer venetoclax tablets by mouth daily. Venetoclax is formulated as 100-mg tablets, so patients will take eight 100-mg tablets QD to receive an 800-mg dose. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the patient's first meal of the day (e.g., breakfast).

On days that predose pharmacokinetic (PK) sampling is required, the patient's first meal of the day (e.g., breakfast) will be provided in the morning at the clinic, and venetoclax dosing will occur in the clinic after completion of the meal to facilitate PK sampling.

On days when both venetoclax and fulvestrant are given, the order of study treatment administration will be venetoclax followed by fulvestrant (there is no minimum time required between the administration of venetoclax and the start of fulvestrant administration). If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be given and the second dose noted in the drug log. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken. On days when patients are scheduled to have blood samples collected for PK assessments, the time of each dose of venetoclax will be recorded to the nearest minute. Venetoclax must be stored according to labeled storage conditions. There is to be no break between cycles.

As of 8 October 2020, all active patients in the venetoclax plus fulvestrant arm of the study will be requested to discontinue the venetoclax treatment immediately, and will be given the option to continue fulvestrant treatment alone.

4.3.2.2 Fulvestrant

Fulvestrant 500 mg will be administered in the clinic as two 250-mg IM injections on Cycle 1 Days 1 and 15 and then on Day 1 of each subsequent 28-day cycle. For details regarding the dosing instructions and safety profile of fulvestrant, refer to the local fulvestrant package insert or Summary of Product Characteristics.

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the adverse event observed is not thought to be fulvestrant-related. See Section 5.1.3 for guidelines for treatment interruption or discontinuation of fulvestrant.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (venetoclax and fulvestrant) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.4 Continued Access to Venetoclax

The Sponsor will offer continued access to Roche IMP (venetoclax) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMP (venetoclax) after completing the study if all of the following conditions are met:

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

A patient will not be eligible to receive Roche IMP (venetoclax) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for ER+, HER2-negative locally advanced or MBC
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for ER+, HER2-negative locally advanced or MBC.
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

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

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

4.4.1 Permitted Therapy

Concomitant therapy includes any prescription medication, over-the-counter preparations, herbal or homeopathic remedies, and nutritional supplements used by a patient from 28 days prior to the screening visit through to Study completion/early termination. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

Patients who experience toxicities should be treated symptomatically as clinically indicated. Patients treated with anti-seizure medications, for reasons other than CNS metastases, should have levels monitored regularly. Patients who require maintenance therapy, as specified in the eligibility criteria (see Section 4.1.1 and Section 4.1.2), should continue to receive maintenance therapy.

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used as per standard clinical practice before subsequent doses of study drug. Anti-emetic therapy should be administered per institutional guidelines.

Pain medications administered per standard clinical practice are acceptable while the patient is enrolled in the study.

Bisphosphonate therapy or denosumab for bone metastases are permitted.

4.4.2 Prohibited and Cautionary Therapy

Patients who require the use of any of the excluded therapies listed below will be discontinued from study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 28 days following the patient's last dose of study treatment.

Use of the following therapies is prohibited 21 days prior to first dose of venetoclax or fulvestrant and during the study:

- Radiotherapy (other than palliative radiotherapy to non-target sites)
- Chemotherapy (prior chemotherapy in the locally advanced or metastatic setting is an exclusion criteria; see Section 4.1.2)
- Immunotherapy

- Hormone therapy (other than LHRH agonists [e.g., goserelin injections] for ovarian suppression in premenopausal women)

Steroid therapy for anti-neoplastic intent, with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids, are not permitted during the study at any time.

Other treatments not part of the protocol-specified anti-cancer therapy are not permitted.

Any exceptions must be discussed with the Medical Monitor prior to initiation.

4.4.2.1 Patients Randomized to Receive Venetoclax + Fulvestrant

The following concomitant medications are not allowed within 7 days prior to the administration of the first dose of study drug and should be avoided during venetoclax administration:

- Strong and moderate CYP3A inducers (see Appendix 3 for examples)
- Strong and moderate CYP3A inhibitors (see Appendix 3 for examples)
- If these medications cannot be avoided during the study, the Medical Monitor must be contacted. Strong or moderate CYP3A inhibitor use would require venetoclax dose reduction under the guidance of the Medical Monitor (Appendix 10).

Warfarin may be co-administered with venetoclax with caution and with the guidance of the Medical Monitor (additional INR monitoring may also be required).

A sample list of cautionary and avoided medications that fall into the categories within this section can be found in Appendix 3. It is not possible to produce a 100% exhaustive list of medications that fall into these categories; therefore, if in question, refer to the appropriate product label.

The administration of live, attenuated influenza vaccine (e.g., FluMist®) is prohibited during treatment and within 28 days following the last dose of venetoclax.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential DDIs are generally unknown.

4.4.3 Prohibited Food

Use of the following foods by patients randomized to receive venetoclax + fulvestrant is prohibited for at least 3 days prior to initiation of venetoclax treatment, throughout venetoclax administration and for 28 days after last dose of study treatment.

Constituents of these foods have been shown to inhibit CYP3A4, the major enzyme responsible for the metabolism of venetoclax. Consumption of these foods could lead to increased venetoclax exposure:

- Grapefruit
- Grapefruit products
- Seville oranges (including marmalade containing Seville oranges)
- Star fruit

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities must be performed and documented for each patient.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

Patients who do not initially meet all eligibility criteria may be re-screened once, given that the reason for screening failure was not ER or HER-2 status. Re-screening refers to repeating the entire screening process. Re-screening must occur within 2 weeks of the initial screening, and each patient must be re-consented before re-screening occurs. It will not be considered a re-screening if blood samples have to be redrawn because of sample handling problems, breakage, sample integrity, or laboratory error. Discuss with the Medical Monitor for further guidance.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 28 days prior to the screening visit will be recorded.

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

4.5.3 Physical Examinations

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

An assessment of the patient's ECOG Performance Status (see Appendix 6) will be completed at screening and as specified in the schedule of activities (see Appendix 1). It is recommended, where possible, that a patient's performance status be assessed by the same person throughout the study.

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

Height, weight, and BSA will be measured at Screening; weight and BSA are to be measured as clinically indicated during the study based on findings of the limited, symptom-directed physical examinations.

As part of tumor assessments, physical examinations should also include the evaluation of the presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

4.5.4 Vital Signs

Vital signs will include measurements of body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position.

4.5.5 Tumor and Response Evaluations

All known sites of disease must be assessed per RECIST v1.1 and documented at screening (within 28 days prior to Cycle 1 Day 1) and re-assessed at each subsequent tumor evaluation (every 8 weeks [±5 days] from the date of randomization until Week 24 [±5 days] and every 12 weeks [±5 days] thereafter). Tumor assessments should be performed on this schedule regardless of dose delay until disease progression. In case of early discontinuation, only the patients who discontinue study treatment early without progression and who have not started follow-on treatment will remain on the study's schedule of assessments for progression. Patients who progress or discontinue early without progression but who have initiated a new treatment will remain on the study for OS.

Screening assessments must include computed tomography (CT)/magnetic resonance imaging (MRI) scans of the chest, abdomen, and pelvis; CT/MRI scans of the neck and brain imaging should be included if clinically indicated. A documented SOC tumor assessment performed within 28 days prior to Cycle 1 Day 1 may be used for the

screening assessment provided it meets the above requirements. CT scans should be performed with a contrast agent. For patients with known allergies to the contrast media, it is acceptable to perform a chest CT scan without contrast and an MRI scan for the abdomen (ideally at baseline and every tumor assessment thereafter).

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

Response assessment will be made by the investigator on the basis of physical examinations, CT scans, or MRI, and/or bone scans using criteria outlined in RECIST v1.1 (Appendix 4). The same radiographic procedure used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator to ensure internal consistency across visits.

CT scans throughout the study should include chest, abdomen, and pelvic scans. CT scans of the neck and brain imaging should be included if clinically indicated. At the investigator's discretion, CT scans may be repeated at any time if progressive disease (PD) is suspected.

4.5.5.1 Bone Lesions Assessments

Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions. The special considerations regarding the measurability of bone lesions are outlined in RECIST v1.1 (see Appendix 4).

Bone scans should be performed within 28 days prior to Cycle 1 Day 1. Positive areas on bone scans must be assessed by either **CT scan with bone windows, MRI,** or **X-ray** prior to randomization.

Bone lesions identified at baseline by CT scan, MRI, or X-ray should be assessed using the same modality (CT scan, MRI, or X-ray) and following the same schedule for measurable lesions until disease progression, as described above. Additional bone scans should be performed if clinically indicated. If a bone scan cannot be performed during the course of the study due to, for example, a Technetium-99m shortage, alternative imaging options should be discussed with the Sponsor (e.g., sodium fluoride).

Abnormalities found on subsequent bone scans must also be confirmed by CT scan, MRI, or X-ray assessment.

If the patient presents with both irradiated and non-irradiated bone lesions, only the non-irradiated lesions should be followed for tumor assessments unless progression is

documented after the radiation. In patients without bone-only disease, bone scans should be repeated in the event of a clinical suspicion of progression of existing bone lesions, the development of new bone lesions, and in the assessment of a complete response (CR), if any disease was evident at screening. Any changes in bone imaging should be evaluated radiographically by CT scan, MRI, or X-ray to ascertain the presence of bone destruction versus a healing reaction.

In the event that it is not feasible to perform a bone scan or it is anticipated that it will not be feasible to perform bone scans throughout the study, 18^{F} sodium fluoride (NaF) PET bone scans may be substituted, with the Sponsor's approval. The same modality used at screening should be used throughout the study.

Patients with symptoms of rapidly progressing disease without radiological (or photographical) evidence will not be considered to have progressed for efficacy analyses. The evaluation of overall lesion response will be performed according to RECIST v1.1 as described in Appendix 4.

4.5.5.2 Tumor Scans

To ensure a valid comparison of tumor data and uniformity in the assessment of tumor response during the study, the following procedures must be implemented at the study site:

- All lesions identified at baseline (target and non-target) will be reassessed using the same method throughout the course of the study.
- All CT scans and MRIs obtained for all patients enrolled at the center should be reviewed by the local radiologist who, together with the investigator, will determine the local assessment of response and progression. All bone scans obtained from the patient with bone metastases at baseline also should be reviewed similarly.
- For patients with measurable disease at baseline, tumor response and progression will be determined by the investigator according to RECIST v1.1 criteria and will be the basis for the efficacy analyses.

Only the patients who discontinue study treatment early without progression and who have not started follow-on treatment will continue to undergo tumor-response evaluations until PD.

4.5.6 Other Disease-Specific Assessments

Tumor samples from the primary tumor (or metastatic site, in the absence of primary site) are to be assessed for expression of BCL-2 and other markers of breast disease biology (i.e., ER, PR, HER2, Ki67, and other BCL-2 family members), mutations in cancer-related genes assessed by NGS of DNA and expression of cancer-related genes assessed by quantification of RNA.

- ER-positive status will be determined prior to study entry by local laboratory testing using IHC per ASCO/CAP criteria (Hammond et al. 2010)

- HER2-negative disease status will be determined prior to study entry by local laboratory testing as per the ASCO/CAP criteria (Wolff et al. 2013). Patients who were originally diagnosed with HER2-positive breast cancer that converted to HER2-negative MBC are NOT eligible to take part in this study.
- BCL-2 expression status will be determined prior to study entry by central laboratory testing using the Ventana BCL-2 IHC assay. BCL-2 high is defined as ≥50% of tumor cells stained with an intensity of IHC 2+ or 3+, and BCL-2 low is defined as ≥50% stained with an intensity of IHC 0 or 1^{+}, and < 50% stained an intensity of IHC 2+ or 3+.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for hematology, blood chemistries, and urinalysis will be analyzed at the study site's local laboratory. Samples for biologic markers and pharmacokinetics will be sent to one or more central laboratories or to the Sponsor or designee for analysis. Samples will be collected as per the schedule of activities in Appendix 1.

Instruction manuals and supply kits will be provided for all central laboratory assessments.

Laboratory assessments will include the following:

- Hematology: hemoglobin, hematocrit, RBC count, platelet count, WBC count, and WBC differential count (neutrophils, bands [optional], lymphocytes, eosinophils, basophils, monocytes), and absolute counts
- Chemistry: sodium, potassium, chloride, random glucose, BUN, creatinine, ALT, AST, total bilirubin, amylase, lipase, total protein, albumin, calcium, phosphorus, LDH, CK, gamma-glutamyl transferase, alkaline phosphatase (ALP), and uric acid

  To evaluate any possible risk of TLS with venetoclax in patients with ER-positive breast cancer, the first 10 patients enrolled into each arm will have a sample collected for a serum chemistry panel 24 hours after the first dose of study drug.
- Coagulation: INR or aPTT (or PTT) required for all patients within 14 days prior to Cycle 1 Day 1 and then as clinically indicated
- Urinalysis: Specific gravity, pH, glucose, protein, ketones, and blood

  Urinalysis is required for all patients within 28 days prior to Cycle 1 Day 1 and then as clinically indicated
- Viral serology: hepatitis B (HBsAg) or hepatitis C (HCV antibody)

  Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation.

  Patients with a past or resolved HBV infection (defined as having a positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.
- Pregnancy test:

Women of childbearing potential (defined in Section 4.1.1) must have a negative serum pregnancy test result at screening within 14 days prior to the first study drug administration.

The urine pregnancy tests should be repeated during the treatment period within 3 days prior to each cycle (every 28 days starting on Day 1 of Cycle 2), at the study discontinuation visit, and as clinically indicated.

– Any positive urine pregnancy test must be confirmed with a serum *β*-hCG evaluation at the local laboratory. Pregnancy test results must be available prior to the administration of fulvestrant.

For all other women, documentation must be present in the medical history confirming that the patient is not of childbearing potential.

The following samples will be sent to the Sponsor or a designee for analysis.

- Plasma PK assessments for venetoclax. See the Schedule of Pharmacokinetic Samples provided in Appendix 2 for specific timepoints.
- Archival or newly collected tumor tissue sample obtained at baseline for determination of expression of BCL-2 by central laboratory testing for patient eligibility purposes and for exploratory research on biomarkers

  A representative FFPE tumor specimen in a paraffin block (preferred) or at least 20 slides containing unstained, freshly cut, serial sections must be submitted along with an associated pathology report prior to study enrollment. If only 10−19 slides are available, the patient may still be eligible for the study, after Medical Monitor approval has been obtained.

  Tumor tissue should be of good quality based on total and viable tumor content. Samples must contain a minimum of ≥20% viable tumor cells that preserve cellular context and tissue architecture regardless of needle gauge or retrieval method. Samples collected via resection, core-needle biopsy (at least three cores, embedded in a single paraffin block), or excisional, incisional, punch, or forceps biopsy are acceptable. Fine-needle aspiration (defined as samples that do not preserve tissue architecture and yield cell suspension and/or smears), brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. Tumor tissue from bone metastases that have been decalcified is not acceptable.

  If archival tumor tissue is unavailable or is determined to be unsuitable for required testing, a pretreatment tumor biopsy is required. A pretreatment tumor biopsy may also be performed if a patient's archival tissue test results do not meet eligibility criteria.

Exploratory biomarker research may include, but will not be limited to, analysis of ctDNA (i.e., mutation profiles associated with palbociclib, that is, cyclin 4/6, ER, or BCL-2 family), and genes or gene signatures associated with apoptosis (i.e., BCL-2 family or immunobiology), and may involve extraction of DNA, ctDNA, or RNA, analysis of somatic

mutations, and use of WTS, or NGS. NGS methods will not include whole genome sequencing (WGS) or whole exome sequencing (WES).

NGS may be performed by Foundation Medicine. If performed by Foundation Medicine, the investigator can obtain results from these analyses in the form of an NGS report, which is available upon request directly from Foundation Medicine. If allowed by local laws, the investigator may share and discuss the results with the patient, unless the patient chooses otherwise. The Foundation Medicine NGS assay has not been cleared or approved by health authorities. The NGS report is generated for research purposes and is not provided for the purpose of guiding future treatment decisions. Results may not be available for samples that do not meet testing criteria.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Plasma samples collected for PK analysis may be needed for additional PK assay development and validation; therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Plasma and tumor tissue samples collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- For enrolled patients, remaining archival tissue blocks will be returned to the site upon request or 18 months after final closure of the study database, whichever occurs first. For patients who are not enrolled, remaining archival tissue blocks will be returned to the site no later than 6 weeks after eligibility determination.

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis will be subject to the confidentiality standards described in Section 8.4.

4.5.8 Electrocardiograms

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 10 minutes.

All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and QT interval corrected through use of Fridericia's formula (QTcF) based on the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If at a particular postdose timepoint the mean QTcF is $>$500 ms and/or $>$60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. SOC treatment may be instituted per the discretion of the investigator. If a PK sample is not scheduled for that timepoint, an unscheduled PK sample should be obtained. A decision on study drug discontinuation should be made, as described in Section 5.1.3.2. The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.9 Patient-Reported Outcomes

4.5.9.1 EORTC QLQ-C30 Background

The EORTC QLQ-C30 (see Appendix 5) is a validated and reliable self-reported measure (Aaronson et al. 1993; Sprangers et al. 1996; Fitzsimmons et al. 1999) consisting of 30 questions that assess 5 aspects of patient functioning (physical, emotional, role, cognitive, and social), 8 symptoms (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea), financial difficulties, and GHS/HRQoL with a recall period of the previous week. The EORTC QLQ-C30 data will be scored according to the EORTC scoring manual (Fayers et al. 2002). Scale scores will be obtained for each of the multi-item and single-items scales by using a linear transformation for standardization of the calculated raw score. The EORTC QLQ-C30 takes approximately 10 minutes to complete.

To fully characterize venetoclax with fulvestrant compared with single-agent fulvestrant as a second-line treatment in patients with MBC, PRO data will be collected using the EORTC QLQ-C30. Specifically, the GHS/overall HRQoL scale score (Questions 29 and 30) will be used to assess patients' overall HRQoL and the pain (Questions 9 and 19)

scale of the EORTC QLQ-C30 will be used evaluate the proportion of patients with disease-related pain of venetoclax+fulvestrant compared with fulvestrant alone.

The EORTC QLQ-C30 will be administered to patients to assess pain, disease/treatment-related symptoms, functioning, and HRQoL (see Section 4.5.9.2 and Appendix 5).

4.5.9.2 EORTC QLQ-C30 Procedures

The EORTC-QLQ-C30 must be administered at the pre-specified clinic visits, and the questionnaire must be completed by the patient at the investigational site at the start of the clinic visit prior to receiving information on disease status, prior to any other study assessments, and before administration of study treatment. Patients will complete paper versions of the questionnaire, which will be provided by site staff. Interviewer assessment is allowed but can only be conducted by a member of the clinic staff for patients who are unable to complete the measures on their own. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site. Appropriate translated versions of the local language of the PRO measures will be available at the site.

4.5.10 Optional Tumor Biopsies

Consenting patients will undergo optional tumor biopsies at Cycle 3 Day 1 (±3 days) after treatment initiation and at disease progression and may undergo additional on-treatment biopsies at any other time at the investigator's discretion (if deemed clinically feasible by the investigator). Where fresh biopsy is possible, samples collected via resection, core-needle biopsy, or excisional, incisional, punch, or forceps biopsy are acceptable. (Note: biopsies collected via fine-needle aspirations are not acceptable.) For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

The Informed Consent Form will contain a separate section that addresses optional biopsies. A separate, specific signature will be required to document a patient's agreement to undergo optional biopsies. The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the Optional Biopsy Sample Informed Consent eCRF. Samples may be used for exploratory biomarker research as described in Section 4.5.7.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

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

- Investigator or Sponsor determines it is in the best interest of the patient (including high-grade toxicities when continuing treatment is deemed detrimental)
- Pregnancy
- Use of an anti-cancer therapy not required per protocol
- Disease progression

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit 28 days (+3 days) after the last dose of study drug (see Appendix 1 for additional details).

After treatment discontinuation due to disease progression, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every *3 months, or more frequently,* until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are discontinued from study treatment for reasons other than disease progression and have started follow-on treatment/s will be followed for survival approximately every *3 months, or more frequently,* until death, lost to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

Patients who are discontinued from study treatment/s for reasons other than disease progression and have not started follow-on treatment/s will be followed for disease status every 8 weeks (±5 days) from the date of randomization until Week 24 (±5) days and every 12 weeks (±5 days), thereafter, until disease progression, loss to follow-up, withdrawal of consent, death or study termination by the Sponsor, whichever occurs first (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the

appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

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

4.6.3 Study Discontinuation

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

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

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Venetoclax was granted approval in the United States (see Venclexta® U.S. Prescribing Information 2016) and conditional market approval by the EMA (see Venclyxto® EMA Summary of Product Characteristics 2016) as monotherapy for the treatment of patients with CLL who have 17p deletion.

Venetoclax, however, is not approved for the treatment of breast cancer, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with venetoclax in completed and ongoing studies. The anticipated important safety risks for venetoclax are outlined below. Please refer to the Venetoclax Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for

toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Venetoclax

Clinical experience gained thus far with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the Venetoclax Investigator's Brochure for more information. On the basis of clinical data to date, the following known and potential risks with venetoclax are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.3.

5.1.1.1 Tumor Lysis Syndrome

The available data suggest that in patients with non-CLL, with the exception of those with mantle cell lymphoma, the risk of TLS is low. Due to different biology between ER+ breast cancer and hematological malignancies, the risk of TLS is considered to be very low in patients with ER+ breast cancer. Therefore, TLS prophylaxis is not recommended by any of the international guidelines for patients with ER+ breast cancer, even in those patients who have developed visceral crisis and are receiving chemotherapy.

The target population in this trial is considered to have low disease burden compared with patients who have visceral crisis and therefore TLS risk is negligible. Nevertheless, patients should be advised to remain well hydrated for the first week of study drug administration. Although not mandatory, at the discretion of the investigator, a prophylactic oral agent (e.g., allopurinol 300 mg QD) may be initiated in patients who are deemed to be at the risk of TLS in order to reduce the uric acid level. Laboratory values obtained before the dose of venetoclax are to be used to determine whether a patient developed a change related to TLS. Laboratory results of the 24-hour postdose must be reviewed before receiving the dose of venetoclax for that day. Patients who develop electrolyte changes suggestive of TLS should undergo aggressive management and further monitoring per Appendix 9.

Patients with TLS should be treated as per institutional practice and local guidelines, including correction of electrolyte abnormalities and monitoring of renal function and fluid balance. Recommendations for initial management of electrolyte imbalances and prevention of tumor lysis syndrome are provided in Appendix 8. In some cases, dialysis may be indicated. Guidelines for defining TLS are provided in Appendix 9.

To evaluate any possible risk of TLS with venetoclax in patients with ER+ breast cancer, the first 10 patients enrolled into each arm of the study will each have a sample collected for a serum chemistry panel 24 hours after the first dose of study drug. The IMC will convene after 5 patients are enrolled in each arm to review the chemistry panel results and establish a management plan for TLS if an increased risk is identified, if needed.

5.1.1.2 Neutropenia

Neutropenia is an important identified risk for venetoclax. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in Table 3. Granulocyte colony stimulating factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infection.

5.1.1.3 Infections

Infections have been reported in oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated patients with hematologic malignancies and are similar across all indications.

Patients in this study will be closely monitored for infections and prompt therapy will be instituted as necessary as per local SOC.

5.1.1.4 Other Hematological Effects

Anemia has been reported across oncology studies investigating venetoclax, with a higher frequency in some studies in which venetoclax is combined with other reference therapies; however, most of the events were non-serious and confounded by disease factors and prior therapies.

Thrombocytopenia adverse events have been reported in oncology studies investigating venetoclax, with a higher frequency in those studies in which venetoclax was combined with other chemotherapeutic agents. However, most of the events were non-serious and assessment of these events is confounded by the patients' underlying hematologic malignancy disease state, prior therapies, and preexisting thrombocytopenia, including autoimmune thrombocytopenia in several patients.

Lymphopenia has been observed in nonclinical studies and in the Phase I clinical study conducted in heavily pretreated patients with CLL and NHL. While opportunistic infections have been reported in the clinical program, data are confounded by the patients' underlying disease and prior therapies. Patients in this study who develop lymphopenia are potentially at risk for atypical infections. As such, prophylaxis against varicella zoster virus and *Pneumocystis jiroveci* pneumonia should be considered and implemented (if applicable) as per local institutional practice, although some guidance is provided in Appendix 7.

5.1.1.5 Reproductive System Effects and Pregnancy

This study enrolls only female patients. The effect of BCL-2 inhibition on pregnancy has not been fully characterized. In animal studies, venetoclax resulted in increased post-implantation loss, and decreased fetal body weights were observed in the mouse embryo-fetal development study at the highest dosage administered. Venetoclax was not teratogenic.

Two human pregnancies have been reported in the clinical program with venetoclax so far, including one pregnancy of a partner; in both cases, a live infant with no neonatal complication, congenital anomalies, or birth defects was delivered.

In nonclinical studies, both venetoclax and fulvestrant have shown a potential to cause reproductive and embryo-fetal developmental toxicities as single agents. Therefore, there is the potential for this combination to cause overlapping or additional reproductive and embryo-fetal toxicities than the individual molecules. Consequently, both venetoclax and fulvestrant should not be administered to pregnant women, and they must be discontinued if a patient becomes pregnant. Additionally, patients are advised to remain abstinent (i.e., refrain from heterosexual intercourse) or use non-hormonal contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for *up to 2 years* after the last dose of study drug *(or based on the local prescribing information for fulvestrant)*. Please refer to Section 4.1.1 for further details on study eligibility and contraceptive requirements for patients.

5.1.1.6 Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies have been reported across the venetoclax hematologic oncology program. However, no causal association with the venetoclax administration has been confirmed, and no pattern has been observed. The overall observed incidence rate of malignancy in the venetoclax clinical trial programs were comparable to that reported in the general population. The second primary malignancies will be closely monitored in this study.

5.1.1.7 Food Effect

Administration with a low-fat meal increased venetoclax exposure by approximately 3.4-fold and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions. Venetoclax should be administered with a meal as described in Section 4.3.2.1.

5.1.1.8 Concomitant Use with Other Medications

Specific recommendations are provided for co-administration of venetoclax with other medications, including inhibitors and inducers of CYP3A (see Section 4.4).

Live, attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization

with live, attenuated vaccines during or following venetoclax therapy have not been studied. Patients should be advised that vaccinations may be less effective.

Due to possible CYP3A mediated metabolic interaction, certain food items (e.g., grapefruit and Seville oranges) should not be consumed during treatment with venetoclax. Further details of excluded food items are provided in Section 4.4.

5.1.2 Safety Plan for Fulvestrant

Fulvestrant is an ER antagonist indicated for the treatment of HR+ MBC in postmenopausal women with disease progression following anti-estrogen therapy.

In a study with postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease, the most frequently reported adverse events were injection-site pain (11.6% of patients), nausea (9.7%), and bone pain (9.4%). Because fulvestrant is administered intramuscularly, it should be used with caution in patients with bleeding diatheses, thrombocytopenia, or anticoagulant use. For details regarding the safety profile of fulvestrant, refer to the local prescribing information.

There are no expected clinically significant overlapping toxicities between venetoclax and fulvestrant. Routine safety monitoring and periodic laboratory tests for the fulvestrant and venetoclax combination will occur throughout the study.

Fulvestrant should not be administered to pregnant women and it must be discontinued if a female patient becomes pregnant. Please refer to Section 4.1.1 and Section 4.1.2 for further details on study eligibility and contraceptive requirements for patients.

5.1.3 Management of Patients Who Experience Specific Adverse Events

5.1.3.1 Dose Modifications

The fulvestrant dose level cannot be modified. In general, the investigator may consider continuing fulvestrant if the observed adverse event is not thought to be fulvestrant-related.

See Section 5.1.3.3 for dose delay or modification guidelines of venetoclax.

5.1.3.2 Treatment Interruption

Patients who interrupt all study treatments secondary to treatment-related adverse events for longer than 28 days should discontinue all study drugs, although they are to continue being followed for disease progression as described in Appendix 1. However, patients who are deriving benefit from the treatment may continue treatment at the investigator's discretion based upon the risk/benefit balance.

As of 8 October 2020, venetoclax will no longer be administered to patients in the study.

Patients who discontinue fulvestrant should also discontinue venetoclax, although they are to continue evaluation per protocol.

5.1.3.3 Management Guidelines

Guidelines for management of specific adverse events are outlined in Table 3. Recommendations for the initial management of electrolyte imbalances and prevention of TLS are provided in Appendix 8. Additional guidelines are provided in the subsections below.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events

Event	Action to Be Taken
Grade 3 or 4 (NCI grading scale) neutropenia with or without fever and infection	• Withhold venetoclax for at least 7 days. • Administer treatment including G-CSF or growth factors for neutropenia as indicated. • When counts recover to ANC $\geq 1 \times 10^9$/L resume venetoclax at one dose-level reduction.
Grade 3 thrombocytopenia with symptomatic bleeding or Grade 4 thrombocytopenia	• Withhold venetoclax for Grade 4 thrombocytopenia or Grade 3 in presence of symptomatic bleeding until resolution of bleeding. Platelets may be transfused at the discretion of the investigator. When platelet level rises to ≥75,000/μL without transfusional support, restart venetoclax at previous dose. • For a second episode of severe thrombocytopenia and/or symptomatic bleeding, withhold venetoclax. When platelet level rises to ≥75,000/μL without transfusional support, restart venetoclax at one dose-level reduction. • For subsequent episodes of severe thrombocytopenia, withhold venetoclax. When platelet level rises to ≥75,000/μL without transfusional support, restart venetoclax at one dose-level reduction. • For recurrent severe thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, consult the Medical Monitor regarding continuation on the protocol.
Non-hematologic toxicity	
Grade 3 or 4 non-hematologic events not specifically described above	• Delay venetoclax for a maximum of 28 days. First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose-level reduction. • Certain treatment emergent non-hematologic adverse events (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases, if a patient is clinically stable, resumption of study drug may be possible after consultation with the Medical Monitor.

Table 3 Guidelines for Management of Patients Who Experience Specific Adverse Events (cont.)

Event	Action to Be Taken
Grade 2 non-hematologic toxicity	• Delay treatment with venetoclax until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days. • After resolution, resume full dose of venetoclax
Grade 1 non-hematologic toxicity	• There is no dose reduction or delay.

CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte stimulating factor; NCI = National Cancer Institute.

Although patients with adverse events are to be managed according to the particular clinical circumstances based on the investigator's medical judgement, dose reduction of venetoclax by one and, if needed, two dose levels will be allowed depending on the type and severity of the toxicity encountered. Each dose reduction of venetoclax will occur by 200 mg (e.g., the starting dose of 800 mg will be reduced to 600 mg, then to 400 mg. If a third dose reduction is necessary (from 400 mg to 200 mg) this should be discussed with the Medical Monitor. Patients who require venetoclax dose reduction below 200 mg should discontinue venetoclax. Such patients may continue to receive fulvestrant at the discretion of the investigators. Patients requiring clarification regarding management of adverse events and dosing and all patients requiring more than two dose reductions should be discussed with the Medical Monitor. All dose modifications/adjustments must be clearly documented in the patient's source notes and eCRF.

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

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a

pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- TLS

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4, Section 5.5, and Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported through 28 days after the last dose of study drug (venetoclax or fulvestrant, whichever is later). After this period, investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to prior study drug treatment as prescribed in Section 5.6.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE v5.0 will be used for assessing adverse event severity. Table 4 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 4 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 5):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 5 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection-Site Reactions

Adverse events that occur during or within 24 hours after study drug administration and are judged to be related to study drug injection should be captured as a diagnosis (e.g., "injection-site reaction" on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Injection-Site Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Injection-Site Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

For adverse events other than injection-site reactions (see Section 5.3.5.1), a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on

signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

  Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of MBC should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Metastatic Breast Cancer

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. The expected pattern of progression will be supported by radiology assessments as per RECIST v1.1. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., to provide TLS prophylaxis or monitoring without significant clinical sequelae, or to perform an efficacy measurement for the study)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

No safety data related to overdosing of venetoclax are available. Refer to the local fulvestrant package insert for safety information related to fulvestrant.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for an adverse event.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3, see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis

- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and Institutional Review Board (IRB)/Ethics Committee (EC).

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information

Medical Monitor/Roche Medical Responsible: [redacted], *M.D., Ph.D.* (Primary)

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and non-serious adverse events of special interest will be reported through 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should

be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting adverse events that occur more than 30 days after the last dose of venetoclax or fulvestrant are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator must discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

At the time of study treatment completion or study treatment discontinuation, the investigator should instruct each patient to report to the investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

Drug	*Document*
Fulvestrant	***Fulvestrant Summary of Product Characteristics***
Venetoclax plus fulvestrant combination	***Venetoclax Investigator's Brochure for solid tumour studies***

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

Analysis populations are defined as follows:

- The ITT population is defined as all randomized patients whether or not they were assigned to the arm where the study treatment was administered.
- The BCL-2 high population (patients within ITT and with $\geq$50% of tumor cells stained with an intensity of IHC 2^+ or 3^+) or BCL-2 low population (patients within ITT and with BCL-2 $\geq$50% stained with an intensity of IHC 0 or 1+ and $<$ 50% stained an intensity of IHC 2^+ or 3^+).
- The safety-evaluable population is defined as patients who received any amount of any component of the investigational or non-investigational study treatments.

The ITT population is the primary analysis population for the study.

6.1 DETERMINATION OF SAMPLE SIZE

Approximately 100 patients need to be recruited and randomized in a 1:1 ratio to two treatment arms (venetoclax + fulvestrant and fulvestrant). The study will enroll both BCL-2 high ($\geq$50% of tumor cells stained with an intensity of IHC 2+ or 3+) and low

(≥50% of tumor cells stained with an intensity of IHC 0 or 1+ and < 50% IHC 2+ or 3+) patients, and it is planned to enroll approximately 50 BCL-2-high patients.

The sample size of 100 patients provides precision of 15% for 80% CI when calculating the absolute difference in the CBR between the two arms assuming the expected observed CBR in the control arm is 40% (Cristofanilli et al. 2016) and in the venetoclax arm is 60% (i.e., the 80% CI for difference in CBR is from 5% to 35%).

6.2 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, duration of follow-up, and discontinuation from the study and reasons for discontinuation will be summarized by treatment arm for all randomized patients. In addition, major protocol violations will be summarized by treatment arm.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, race, lines of prior therapy in the locally advanced/metastatic setting, BCL-2 status, sites of disease [bone vs. nodal vs. visceral], previous endocrine therapy type [AI vs. tamoxifen vs. combination], menopausal status [pre-/perimenopausal vs. postmenopausal]), will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Summaries will be presented overall and by treatment group.

6.4 EFFICACY ANALYSES

Patients will be analyzed in accordance with the treatment arm to which they were randomized.

The primary analysis will be conducted when all patients have discontinued from study treatment, or 6 months after last patient in, whichever occurs first.

6.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is clinical benefit, defined as CR, partial response (PR) or SD lasting ≥24 weeks from randomization in patients with measurable disease at baseline, as determined by the investigator according to RECIST v1.1. Patients with no response assessments for any reason will be considered non-responders.

The CBR analysis will be conducted for the ITT population, the BCL-2 high subgroup, and the BCL-2 low subgroup. The CIs for the difference in CBR between the two treatment arms will be determined using the normal approximation to the binomial distribution. An estimate of the CBR and its 95% CI will be calculated for each treatment arm.

6.4.2 Secondary Efficacy Endpoints

6.4.2.1 Progression-Free Survival

PFS is defined as the time from randomization to the first occurrence of disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first. Data for patients without the occurrence of disease progression or death as of the clinical data cut-off date will be censored at the time of the last tumor assessment (or at the time of randomization plus 1 day if no tumor assessment was performed after the baseline visit).

The Kaplan-Meier approach will be used to estimate median PFS for each treatment arm. The Cox proportional hazards model and its 95% CI, stratified by lines of prior therapy (one vs. two) and BCL-2 status (high vs. low), will be used to estimate the hazard ratio between the two treatment arms. The unstratified hazard ratio will also be provided.

6.4.2.2 Objective Response

The objective response (OR) is defined as PR or CR, which is determined by the investigator according to RECIST v1.1. Patients without post-baseline information will be counted as non-responders.

The same analyses for CBR will be conducted on the objective response rate.

6.4.2.3 Duration of Objective Response

Duration of response (DOR) is defined as time from the first occurrence of a documented objective response to the time of the first documented disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first. Data for patients without the occurrence of disease progression or death as of the clinical data cut-off date will be censored at the time of the last tumor assessment.

DOR will be estimated using the Kaplan-Meier methodology, with patients grouped according to the treatment arm assigned at randomization. Only patients achieving a CR or PR will be included in the assessment of DOR.

6.4.2.4 Overall Survival

OS is defined as the time from randomization to death from any cause. Data for patients who are alive at the time of the analysis data cut-off will be censored at the last date they were known to be alive. Data from patients without postbaseline information will be censored at the date of randomization plus 1 day.

The same analyses for PFS will be conducted for OS.

6.5 SAFETY ANALYSES

The safety analyses will include all randomized patients who received at least one dose of venetoclax or fulvestrant (the safety population) with patients grouped according to the treatment actually received.

Drug exposure will be summarized to include duration of treatment, number of doses, and intensity of dose.

All adverse events occurring during or after the first study drug dose will be summarized by treatment arm and NCI CTCAE grade. In addition, serious adverse events, adverse events of special interest, and adverse events leading to study drug discontinuation or interruption will be summarized accordingly. Multiple occurrences of the same event will be counted once at the maximum severity.

Deaths reported during the study treatment period and those reported during the safety follow-up period will be summarized by treatment arm.

6.6 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Sparse PK samples will be collected and analyzed for venetoclax and fulvestrant concentrations in the venetoclax arm. The PK data will be summarized after appropriate grouping. Venetoclax and/or fulvestrant results may be incorporated into a nonlinear mixed-effect population PK model to estimate the PK parameters. Pharmacodynamic modulation of BCL-2 and estrogen-responsive genes will be evaluated in optional on-treatment biopsies relative to pre-dose biopsies.

Additional PK analyses will be conducted as appropriate.

6.7 EXPLORATORY OBJECTIVES

6.7.1 Patient-Reported Outcome Analyses

Summary statistics (i.e., mean, standard deviation, median, minimum, maximum, and range) of linear transformed scores will be reported for all scales (symptom, functional domains, and single items) of the EORTC QLQ-C30 according to the EORTC scoring manual guidelines (Fayers et al. 2002) for each assessment timepoint. Line charts depicting the mean changes $\pm$ *standard deviations* of items and scales over time will be provided for each treatment arm from the baseline assessment.

Previously published minimally important differences will be used to identify meaningful change from baseline within each treatment group on the functional and disease/treatment related symptoms scales (Osoba et al. 1998). In the event of incomplete data, for all questionnaire subscales, if more than 50% of the constituent items are completed, a prorated score will be computed consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

To evaluate patient-reported HRQoL while on study treatment, descriptive analysis of the mean and mean change from patients' baseline GHS/HRQoL scale score, which consists of Questions 29 and 30 of the EORTC QLQ-C30 (see Appendix 5), will be assessed by cycle and independently within each cohort. GHS/HRQoL will also be calculated as the number, proportion, and *95%* CI of patients with a change in score *reflecting clinically meaningful deterioration, defined as a decrease of 10 points or more (Osoba et al., 1998).*

To evaluate patient-reported pain while on study treatment, descriptive analysis of the mean and mean change from patients' baseline pain scale score, which consists of Questions 9 and 19 of the EORTC QLQ-C30 (see Appendix 5), will be assessed by cycle and independently within each cohort. Additionally, the pain scale data will also be calculated as the number, proportion, and *95%* CI of patients with *clinically meaningful* pain progression *defined by an increase in score of 10 points or more (Osoba et al., 1998).*

6.8 BIOMARKER ANALYSES

Exploratory analyses of biomarkers related to tumor biology and the mechanisms of action of venetoclax will be conducted. Analyses will assess prognostic and/or predictive value of candidate biomarkers. The association between candidate biomarker measures of efficacy, with treatment and independent of treatment, will be explored to assess potential predictive and prognostic value, respectively. The effects of baseline prognostic and potentially predictive characteristics, including BCL-2 expression, BCL-2 family member transcript and/or gene signatures, as well as ctDNA profiles on efficacy outcomes, will be evaluated using univariate and/or multivariate statistical methods such as Cox regression and logistic regression.

6.9 OPTIONAL INTERIM ANALYSES

Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct up to two interim efficacy analyses. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis. The interim analysis will be performed and interpreted by members of the Sponsor study team and appropriate senior management personnel.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and any other externally generated electronic study data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 PATIENT-REPORTED OUTCOME DATA

Patients will use paper forms to record PRO data. PROs must be stored in the appropriate patient file as source data and maintained at the study site.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the *applicable* laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) *and applicable local, regional, and national laws.*

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

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

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication (see Section 9.6).

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

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.3).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, PROs, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures,

prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 *MANAGEMENT OF STUDY QUALITY*

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. The Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 centers globally will participate to enroll approximately 100 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be formed to monitor and evaluate patient safety throughout the study, as specified in Section 3.2.

9.6 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses*, in clinical trial registries,* and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. *Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon*

request. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Study Period	Screening [a]	Treatment Period							Study Drug Discontinuation Visit [c]	Off-Tx Follow-Up Visit [d]	Survival Follow-Up Visit [e]
Cycle (Every 28 days (± 3 days of scheduled treatment day)		Cycle 1			Cycle 2	Cycles 3–4	Cycles 5–6	Subsequent Cycles [b]			
Day of Cycle	-28 to -1	1	2 [f]	15	1 (±3)	1 (±3)	1 (±3)	1 (±3)			
Informed consent	x										
Demographic data and menopausal status	x										
General medical history and baseline conditions	x										
ECOG Performance Status	x	x		x	x	x	x	x	x		
Complete physical examination [g]	x										
Limited, symptom-directed physical examination		x	x		x	x	x	x	x	x	
Vital signs [h]	x	x	x	x	x	x	x	x	x	x	
Height	x										
Weight and BSA	x	As clinically indicated									
Bone scan [i]	x										
12-Lead ECG	x										
Tumor or response assessment [j]	x				Every 8 weeks (± 5 days) from the date of randomization until Week 24 (± 5 days) and every 12 weeks (± 5 days) thereafter					x	
PRO assessments [k]		x			x	x	x	x	x		
Drug administration [l]:											
Venetoclax		x									
Fulvestrant		x		x	x	x	x	x			
Local laboratory assessments											
Hematology [m]	x	x		x	x	x	x	x	x	x [n]	

Appendix 1
Schedule of Activities (cont.)

Study Period	Screening [a]	Treatment Period							Study Drug Discontinuation Visit [c]	Off-Tx Follow-Up Visit [d]	Survival Follow-Up Visit [e]
Cycle (Every 28 days (± 3 days of scheduled treatment day)		Cycle 1			Cycle 2	Cycles 3–4	Cycles 5–6	Subsequent Cycles [b]			
Day of Cycle	-28 to -1	1	2 [f]	15	1 (±3)	1 (±3)	1 (±3)	1 (±3)			
Chemistry [o]	x	x	x	x	x	x	x	x	x	x [n]	
Coagulation	x	As clinically indicated									
Urinalysis	x	As clinically indicated									
Viral serology [p]	x										
Serum pregnancy test [q]	x										
Urine pregnancy test [r]					x	x	x	x	x		
Central laboratory assessments:											
Plasma sample for ctDNA [s]		x				x	x		x		
Tumor sample for BCL-2 family expression, ER, and HER2 determination and exploratory biomarkers	x [t]					x [u]			x [v]		
Plasma sample for PK [w]		x			x		x		x		
Concomitant medications [x]	x	x	x	x	x	x	x	x	x	x [y]	
Adverse events	x [z]	x	x	x	x	x	x	x	x	x [y]	x [y]
Survival follow-up and anti-cancer treatment									x^{aa}	x^{aa}	x

ALP = alkaline phosphatase; β-hCG = β-human chorionic gonadotropin; BCL-2 = B-cell lymphoma 2; BSA = body surface area; ctDNA = circulating tumor DNA; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; ER = estrogen receptor; GGT = gamma-glutamyl transferase; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HER2 = human epidermal growth factor receptor; IM = intramuscular; PCR = polymerase chain reaction; PK = pharmacokinetic; PRO = patient-reported outcomes; QLQ-C30 = Quality of Life Questionnaire–Core 30; TLS = tumor lysis syndrome; Tx = treatment.

Appendix 1
Schedule of Activities (cont.)

[a] Patients who do not initially meet all eligibility criteria may be re-screened once within 2 weeks, given that the reason for screening failure was not ER or HER-2 status (see Section 4.5.1).

[b] Patients will continue subsequent cycles every 28 days (± 3 days of scheduled treatment day) until disease progression, death, loss to follow up, withdrawal of consent, or study termination by the Sponsor (Section 3.3), whichever occurs first.

[c] All patients who discontinue study treatment will return for a study drug discontinuation visit 28 days after last dose (up to 3 days of delay [to Day 31] is acceptable)

[d] For patients who discontinue study treatment early for reasons other than disease progression and have not started follow-on treatment. These patients will be followed every 8 weeks (± 5 days) from the date of randomization until Week 24 (± 5 days) and every 12 weeks (± 5 days), thereafter, until disease progression death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first.

[e] Follow-up of survival and anti-cancer treatment will be conducted *approximately* every *3 months, or more frequently,* from disease progression for all patients until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor, whichever occurs first. The same survival follow-up will be done for patients who discontinue study treatment early for reasons other than disease progression and have started follow-on treatment.

[f] Cycle 1 Day 2 (i.e., 24-hour) visit is required only for the first 10 patients enrolled in each arm. A chemistry panel to monitor for TLS (see Section 5.1.1.1) will be collected and must include at least electrolytes, uric acid, phosphorous, calcium, and creatinine levels.

[g] Complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems.

[h] Vital signs to include body temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position. Height and BSA are only required at screening. Subsequent BSA is required if there is a >10% change in weight.

[i] A bone scan is to be performed within 28 days prior to Cycle 1 Day 1. See Section 4.5.5.1 for further instructions.

[j] See Section 4.5.5 for tumor and response evaluation instructions.

[k] PRO assessments will comprise the EORTC QLQ-C30 (see Appendix 5). PRO questionnaires will be self-administered at the start of each pre-specified clinic visit before the patient receives any information on disease status, prior to the administration of any study treatment, and/or prior to any other study assessments.

[l] Drug administration: Venetoclax will be administered on a once daily dosing schedule. On days when both venetoclax and fulvestrant are given, the order of study treatment administration will be venetoclax followed by fulvestrant (there is no minimum time required between the administration of venetoclax and the start of fulvestrant administration). See Section 4.3.2.1 for more details. *As of 8 October 2020, all active patients in the venetoclax plus fulvestrant arm will be requested to discontinue the venetoclax treatment immediately (see Section 3.1).* Fulvestrant 500 mg will be administered in the clinic as two 250-mg IM injections on Cycle 1 Days 1 and 15 and then on Day 1 of each subsequent 28-day cycle.

Appendix 1
Schedule of Activities (cont.)

[m] Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC count, and WBC differential count (neutrophils, bands [optional], lymphocytes, eosinophils, basophils, monocytes). Reporting the differential as absolute counts is preferred, but percentages are accepted. Assessment must be performed within 3 days (with results available) prior to the administration of study medication. If the screening assessments were done within 3 days prior to Cycle 1 Day 1 there is no need to repeat the hematology at Cycle 1 Day 1.

[n] To be collected if the investigator determines that the tests are clinically indicated.

[o] Chemistry includes sodium, potassium, chloride, random glucose, BUN, creatinine, ALT, AST, total bilirubin, amylase, lipase, total protein, albumin, calcium, phosphorus, LDH, CK, GGT, ALP, and uric acid. Assessment must be performed within 3 days (with results available) prior to the administration of study medication. If the screening assessments were done within 3 days prior to Cycle 1 Day 1 there is no need to repeat the chemistry panel at Cycle 1 Day 1.

[p] Viral serology includes HBsAg or HCV antibody. Patients who are positive for HCV antibody must be negative for HCV by PCR to be eligible for study participation. Patients with a past or resolved HBV infection (defined as having a positive total HBcAb and negative HBsAg) may be included if HBV DNA is undetectable. These patients must be willing to undergo monthly DNA testing.

[q] Required for all women of reproductive potential (see inclusion criteria in Section 4.1.1).

[r] For women of childbearing potential (defined in Section 4.1.1), a urine pregnancy test will be repeated during the treatment period within 3 days prior to each cycle (every 28 days starting on Day 1 of Cycle 2), at study discontinuation visit, and as clinically indicated. Any positive urine pregnancy test must be confirmed with a serum β-hCG evaluation at the local laboratory. Pregnancy test results must be available prior to the administration of fulvestrant. Women who have undergone surgical sterilization or are postmenopausal are exempt from pregnancy assessments.

[s] Samples should be collected predose for analysis of circulating tumor markers of response/resistance at baseline (predose) Cycle 1 Day 1, between Cycle 2 Day 15 and Cycle 3 Day 1, between Cycle 4 Day 15 and Cycle 5 Day 1, and at study drug discontinuation visit.

[t] Sample must include a tumor paraffin tissue block or at least 20 unstained slides (sections obtained <3 months) from the tumor tissue block from either the primary tumor or a metastatic site obtained at the time of the most recent progression prior or during screening for this trial. A pathology report should accompany the tissue sample.

[u] Optional on-treatment tumor biopsy to be performed on Cycle 3 Day 1 (± 3 day) only.

[v] Optional tumor biopsy if disease progression is the reason for the patient discontinuing study treatment.

[w] Refer to Appendix 2 for the schedule of PK samples in the venetoclax arm. On days that predose pharmacokinetic sampling is required, the patient's first meal of the day (e.g., breakfast) will be provided in the morning at the clinic and venetoclax dosing will occur in the clinic after completion of the meal.

[x] Concomitant therapy includes any prescription medication, over-the-counter preparations, herbal or homeopathic remedies, and nutritional supplements used by a patient from 28 days prior to the screening visit through to study completion/early termination.

Appendix 1
Schedule of Activities (cont.)

[y] Adverse events possibly related to study drug are to be recorded as well as any concomitant medications used in association with the event.

[z] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported. After initiation of study drug, all adverse events will be reported through 28 days after the last dose of venetoclax or fulvestrant, whichever is later.

[aa] *New anti-cancer therapy after study drug discontinuation should be reported once known.*

Appendix 2
Schedule of Pharmacokinetic Samples in the Venetoclax Arm

Study Visit	Timepoint	Sample (Plasma)	Draw Sequence
Cycle 1, Day 1	4 hours postdose (±10 minutes)	venetoclax PK	1
Cycle 2, Day 1	Predose (within 1 hour before dosing) [a]	venetoclax PK	1
		fulvestrant PK	2
	2 hours postdose (±10 minutes)	venetoclax PK	1
	4 hours postdose (±10 minutes)	venetoclax PK	1
	6 hours postdose (±20 minutes)	venetoclax PK	1
	8 hours postdose (±30 minutes)	venetoclax PK	1
Cycle 6, Day 1	Predose (within 1 hour before dosing) [a]	venetoclax PK	1
		fulvestrant PK	2
Study drug discontinuation/ Early Termination [b]	Anytime during clinic visit	venetoclax PK	1
		fulvestrant PK	2

PK = pharmacokinetic.

Note: For the PK sample, the plasma samples including primary and back-up samples will be collected per procedures outlined in the separate laboratory manual. Detailed instructions for PK plasma sample preparation and shipping will be provided to the study sites in a separate laboratory manual.

Record exact date and time of all PK sample collections (relative to the administration of the study drug being measured).

[a] Record exact date and time of all study drug doses in the dosing diary.

[b] Obtain a PK blood sample if the patient discontinues study drug.

Appendix 3
Sample List of Medications to Avoid or Use with Caution

Strong CYP3A inhibitors: boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole
Moderate CYP3A inhibitors: aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
Strong CYP3A inducers: carbamazepine (Tegretol®), enzalutamine, mitotane, phenytoin, rifampin (Rifadin®), St. John's wort
Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil
Cautionary [a]
Warfarin [b]
P-gp substrates: dabigatran, digoxin, fexofenadine
P-gp inhibitors: amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP substrates: rosuvastatin, sulfasalazine
BCRP inhibitors: curcumin, cyclosporine A, eltrombopag
OATP1B1/1B3 substrates: asunaprevir, atorvastatin, bosentan, cerivastatin, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin acid

BCRP = breast cancer resistance protein; CYP = cytochrome P450; OATP1B1 = organic anion transporter protein 1B1; P-gp = P-glycoprotein.

[a] If a patient requires use of these medications, use with caution and ask the Medical Monitor for guidance.

[b] Closely monitor INR.

Note: This is not an exhaustive list. For an updated list and detailed explanations, see the following website:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

In addition to the medications listed in this table, patients receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruits.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

MEASURABILITY OF TUMOR AT BASELINE

DEFINITIONS

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows.

a. Measurable Tumor Lesions

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

- 10 mm by computed tomography (CT) or magnetic resonance imagining (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

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

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

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

c. Special Considerations Regarding Lesion Measurability

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

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

TARGET LESIONS: SPECIFICATIONS BY METHODS OF MEASUREMENTS

a. Measurement of Lesions

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

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will be considered measurable only when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For

the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion is suggested.

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

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan on the basis of the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

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

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

<u>TUMOR RESPONSE EVALUATION</u>

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Appendix 4
Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (cont.)

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs but, additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

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

Lesions irradiated within 3 weeks prior to Cycle 1 Day 1 may not be counted as target lesions.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

<u>All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements</u>

are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

RESPONSE CRITERIA

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- Complete response (CR): disappearance of all target lesions

  Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $<$ 10 mm.

- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

  The appearance of one or more new lesions is also considered progression.

- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

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

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

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

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

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. Although some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level

  All lymph nodes must be non-pathological in size ($<$10 mm short axis).

- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions

  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease; that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. Although it would be ideal to have objective criteria to apply to non-measurable

disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

Table 1 Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be “unable to assess” since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be “unable to assess” except where there is clear progression. Overall response would be “unable to assess” if either the target response or the non-target response is “unable to assess,” except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

c. Best Overall Response: All Timepoints

The best overall response is determined once all data for the patient is known, and is interpreted as in Table 2. Complete or partial responses may be claimed if the criteria for each are met at a subsequent timepoint ≥ 4 weeks later.

Table 2 Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

d. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The

objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1 and Table 2.

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

If a patient undergoes an excisional biopsy or other appropriate approach (e.g., multiple passes with large core needle) of a new lesion or an existing solitary progressive lesion that following serial sectioning and pathological examination reveals no evidence of malignancy (e.g., inflammatory cells, fibrosis, etc.), then the new lesion or solitary progressive lesion will not constitute disease progression.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of CR if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5
European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Version 3

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

Appendix 5
European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), Version 3 (cont.)

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 6
Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Table 1 ECOG Performance Status

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 or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

Appendix 7
Suggested Guidance for Atypical Infection Prophylaxis Due to Lymphopenia

In patients who develop Grade 3 and 4 lymphopenia, the following recommendations, as well as those in Table 1, are to be followed, but they may be tailored to the patient and her lymphocyte counts:

- *Pneumocystis jiroveci* pneumonia prophylaxis in the form of combination sulfamethoxazole-trimethoprim (Bactrim DS; 800 mg/160 mg) ii tablets Monday, Wednesday, and Friday
- Varicella zoster virus prophylaxis in the form of valaciclovir 500 mg daily

Table 1 Management of Grade 3 and 4 Lymphopenia

Lymphocyte count	Grade (CTCAE 5.0)	Recommendation
LLN–0.8 $\times$ 10^9/L	1	No prophylaxis
$\leq$0.8–0.5 $\times$ 10^9/L	2	Consider prophylaxis if patient will be exposed to further immune-suppressants (e.g., dexamethasone) and/or radiotherapy
$<$0.5–0.2 $\times$ 10^9/L	3	Consider PJP prophylaxis and VZV prophylaxis
$\leq$0.2 $\times$ 10^9/L	4	PJP prophylaxis and VZV prophylaxis strongly recommended.

CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal; PJP = *Pneumocystis jiroveci* pneumonia; VZV = varicella zoster virus.

When the lymphocyte count is $\geq 0.5 \times 10^9$/L, the prophylaxis may be stopped, at the investigator's discretion. At study completion, cessation of prophylaxis can occur when lymphocyte counts normalize.

Appendix 8
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

FIRST DOSE OF VENETOCLAX

- Within the first 24 hours after the first dose, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150–200 mL/hr; not $<$ 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of tumor lysis syndrome is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

In addition to the recommendations for patients receiving first dose of venetoclax:

- For potassium increase $\geq$ 0.5 mmol/L from baseline, or any value $>$ 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of $>$ 0.5 mg/dL AND $>$ 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

Appendix 9
Guidelines for Defining Tumor Lysis Syndrome

All tumor lysis syndrome events should be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 criteria.

Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days after the start of therapy. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (±alkalinization) and a hypouricemic agent(s).

Table 1 Howard Definition of Laboratory Tumor Lysis Syndrome

Laboratory Assessment	Range
Uric acid	>476 μmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/l (<7.0 mg/dL) or ionized calcium <1.12 (0.3 mmol/L) [a]

Note: Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

[a] The corrected calcium level in mg/dL is the measured calcium in mg/dL + (0.8 × [4-albumin in g/dL]).

Appendix 9
Guidelines for Defining Tumor Lysis Syndrome (cont.)

Table 2 Howard Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory tumor lysis syndrome and one or more of the following criteria:
Creatinine[a]: An increase in serum creatinine level of 0.3 mg/dL (26.5 µmol/L); a single value $>$1.5 times the ULN of the age appropriate normal range if no baseline creatinine measurement is available; or the presence of oliguria, defined as average urine output of $<$0.5 mL/kg/hour for 6 hours
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia [b]

ULN = upper limit of normal.

[a] Acute kidney injury is defined as an increase in the creatinine level of $\geq$0.3 mg/dL (26.5 µmol/L) or a period of oliguria lasting $\geq$6 hours. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome.

[b] Not directly attributable to a therapeutic agent.

REFERENCE

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New Engl J Med 2011;364:1844–54.

Appendix 10 Venetoclax Dose Modifications with Concomitant Moderate and Strong CYP3A Inhibitors

Dose Level	Venetoclax Dose (mg) with No Moderate or Strong CYP3A Inhibitor	Venetoclax Dose (mg) if Co-Administered with a Moderate CYP3A Inhibitor	Venetoclax Dose (mg) if Co-Administered with a Strong CYP3A Inhibitor
Starting dose	800	400	200
Dose level –1	600	300	100
Dose level –2	400	200	100
Dose level –3	200	100	Interrupt venetoclax temporarily

CYP = cytochrome P450.