CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1b Study Followed by an Open label, Parallel, Randomized Phase 2 Study Evaluating the Safety, Tolerability and Efficacy of GS-5829 in Combination with Exemestane or Fulvestrant Comparing with Exemestane or Fulvestrant Alone in Subjects with Advanced Estrogen Receptor Positive HER2- Breast Cancer
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City CA, 94404
IND Number:	124032
EudraCT Number:	2016-002365-63
Clinical Trials.gov Identifier:	Not Available
Indication:	Estrogen Receptor Positive Breast Cancer
Protocol ID:	GS-US-350-1937
Clinical Program Manager:	Name: PPD Telephone: PPD Email: PPD
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Protocol Version/Date:	Original: 17 June 2016

CONFIDENTIALITY STATEMENT

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PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
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Study Title:	A Phase 1b Study Followed by a Parallel Randomized Phase 2 Study Evaluating the Safety, Tolerability and Efficacy of GS-5829 in Combination with Exemestane or Fulvestrant Comparing with Exemestane or Fulvestrant alone in Subjects with Advanced Estrogen Receptor Positive HER2-Negative Breast Cancer
IND Number:	124032
EudraCT Number:	TBD
Clinical Trials.gov Identifier:	Not Available
Study Centers Planned:	Approximately 50 centers in the USA and Europe
Objectives:	**The primary objective:** **Phase 1b Dose Escalation** • To characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive Her2-negative breast cancer (ER+/HER2- BrCa) • To determine the Maximum Tolerated Dose (MTD), if not already determined from Study GS-US-350-1599, or the recommended Phase 2 Dose (RP2D) of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa **Randomized Phase 2 Dose Expansion** • To evaluate the efficacy of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa, as measured by progression-free survival (PFS)

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by PFS

Secondary objectives:

Phase 1b Dose Escalation

- To evaluate the pharmacokinetics (PK) of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa, as measured by overall response rate (ORR) and clinical benefit rate (CBR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1. ORR is defined as the proportion of subjects with response (complete response [CR], or partial response [PR]). CBR is defined as proportion of subjects with CR, PR, or stable disease (SD) that lasts for ≥ 24 weeks
- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by ORR and CBR
- To evaluate the safety and tolerability of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa
- To evaluate the safety and tolerability of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa
- To evaluate the overall survival (OS) for subjects with advanced ER+/HER2- BrCa who receive GS-5829 in combination with exemestane or fulvestrant comparing to exemestane or fulvestrant alone

Exploratory objectives:

PPD

Study Design:

Phase 1b Dose Escalation:

Cohorts of postmenopausal women with advanced ER+/HER2- BrCa, for whom no standard curative therapy exists and who are candidates for exemestane or fulvestrant, will be sequentially enrolled at progressively higher dose levels of oral GS-5829 in combination with standard doses of exemestane or fulvestrant. Up to 60 subjects will be enrolled for the Phase 1b Dose Escalation portion of the study. The starting dose of GS-5829 will be either 3.0 mg once daily or a dose level that has been demonstrated to be safe and tolerable based on other ongoing studies (GS-US-350-1599, GS-US-350-1604).

Eligible subjects will be assigned to either Group A or B based on prior treatment and the investigators' decision. Group A will initiate with GS-5829 orally once daily on Cycle 1 Day 1 (C1D1) combined with 25 mg of exemestane administered orally once daily (or in accordance with locally approved labeling). The subject may initiate exemestane any time prior to, or on, C1D1. Group B will initiate GS-5829 orally once daily on C1D1 with fulvestrant administered intramuscularly (in accordance with locally approved labeling) every 28 days (± 3 days). The subject may initiate fulvestrant any time prior to, or on, C1D1. If C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of fulvestrant should be administered on Cycle 1 Day 15.

The doses of GS-5829 for each Dose Level are shown in the table below.

Phase 1b Dose Escalation: Combination of GS-5829 with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

Dose Level	GS-5829 (once daily)	Group A (Exemestane)	Group B (Fulvestrant)**
1*	3 mg	25 mg orally once daily (or in accordance with locally approved labeling)	500 mg intramuscularly day 1, 29 and then every 28 days (or in accordance with locally approved labeling)
2	4 mg		
3	6 mg		
4	9 mg		

* The initial dose level may be higher (4 mg) or lower (2 mg) than Dose Level 1, depending on results from ongoing studies and emerging PK data.

** Subjects initiating fulvestrant on this study on C1D1and not having received any prior dose of fulvestrant should receive a single additional dose of fulvestrant on Cycle 1 Day 15.

Group A and Group B will dose escalate independently of each other; each cohort will consist of 3 newly enrolled subjects who will be treated at the specified dose level. Dose escalation will continue until identification of the MTD of GS-5829, or a RP2D is reached.

After all the subjects in each cohort have been followed for at least 28 days after the first dose of GS-5829, a dose limiting toxicity (DLT) model (Bayesian logistic regression model, Neuenschwander et al. 2008, see Appendix 10) utilizing all available GS-5829 safety data will be built and will provide estimates of DLT rates at all dose levels. The recommended dose from the dose-DLT model for the next cohort will have the highest probability that the DLT rate will fall in the target interval (16%, 33%), and a probability of < 25% that the DLT rate exceeds 33%.

The dose escalation decision and the final decision for the RP2D will be made by the Safety Review Team (SRT), following a review of the model recommendation and all relevant data including safety information, PK, biomarkers, clinical data from evaluable subjects.

The recommended dose of GS-5829 to be combined with exemestane or fulvestrant in the Randomized Phase 2 Dose Expansion part of this study will be determined based on the data available in the Phase 1b Dose Escalation portion of this study and from studies GS-US-350-1599 and GS-US-350-1604. The recommended dose will not exceed the MTD identified by either the Phase 1b Dose Escalation from this study or from studies GS-US-350-1599 and GS-US-350-1604, whichever dose is higher. At least 6 subjects should have already been treated and evaluated at that dose level prior to enrolling subjects in the Randomized Phase 2 Dose Expansion.

Dose Limiting Toxicity (DLT) Definition

A DLT is a toxicity defined below and considered possibly related to GS-5829 if occurring during the DLT assessment window (Day 1 through Day 28) in each combination therapy cohort:

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3)
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)
- Grade ≥ 4 thrombocytopenia (platelet count < 25,000/µL)
- Grade ≥ 3 thrombocytopenia (platelet count <50,000/µL but >25,000/µL) lasting > 7 days despite GS-5829 drug interruption
- Grade ≥ 2 bleeding (e.g. gastrointestinal, respiratory, epistaxis, purpura)

- Grade ≥ 3 or higher non-hematologic toxicity, except:
  - Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy
  - Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy
- Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk
- Treatment interruption of ≥ 7 days due to unresolved toxicity

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and the Gilead medical monitor may take place to determine if this adverse event (AE) should be assessed as a DLT. However, any Grade 3 or Grade 4 elevation in aspartate transaminase (AST) or alanine transaminase (ALT) associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug will be considered a DLT. See Section 3.2 for details.

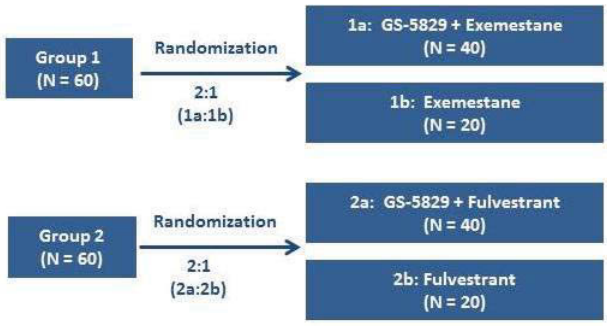
Randomized Phase 2 Dose Expansion:

Approximately 120 female subjects who are post-menopausal with ER+/HER2- BrCa and who have had disease progression following anti-estrogen therapy will be enrolled.

- Approximately 60 subjects who have not previously received exemestane will be randomized in a 2:1 ratio to receive exemestane + GS-5829 or exemestane alone in Group 1.
- Approximately 60 subjects who have not previously received fulvestrant will be randomized in a 2:1 ratio to receive fulvestrant + GS-5829 or fulvestrant alone in Group 2.

GS-5829 and the anti-estrogen therapy (exemestane for Group 1 or fulvestrant for Group 2) will be initiated on C1D1.

Study Schema: Randomized Phase 2 Dose Expansion:



Number of Subjects Planned:

Phase 1b Dose Escalation: Up to 60 subjects will be enrolled

Randomized Phase 2 Dose Expansion: Approximately 120 subjects will be enrolled, with 60 subjects in Group 1 (GS-5829+exemestane vs. exemestane alone) and 60 subjects in Group 2 (GS-5829+fulvestrant vs. fulvestrant alone).

Target Population:

Postmenopausal women with histologically or cytologically confirmed ER+/HER2- BrCa who have progressed after treatment with an anti-estrogen therapy and are candidates for fulvestrant or exemestane therapy.

Duration of Treatment:

Subjects may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death whichever comes first.

Diagnosis and Main Eligibility Criteria:

<u>Inclusion Criteria:</u>

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) ≥18 years of age, female
2) Histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent and who have progressed during treatment with at least one prior hormonal therapy. **Note:** In referring to prior hormonal therapy; targeted therapies, such as palbociclib and/or everolimus or investigative targeted therapies which were administered as part of a prior hormonal therapy regimen are allowed after the washout period has been reached.
    a) Phase 1b Dose Escalation - Subjects may have had unlimited prior hormonal therapy and a total of 2 prior chemotherapy regimens (adjuvant chemotherapy is considered 1 regimen).

Subjects may have progressed on fulvestrant or exemestane as a single agent.

b) Randomized Phase 2 Dose Expansion - Subjects may have had unlimited prior hormonal therapy, only one adjuvant chemotherapy is permitted (no prior chemotherapy for metastatic disease is allowed). Subject enrolling in Group 1 must be exemestane naïve and subjects enrolling in Group 2 must be fulvestrant naïve. If a subject is naïve to both exemestane and fulestrant, it is the investigator's decision for which Group to enroll.

3) Documentation of ER positive (≥ 1% positive stained cells by local standards) based on the most recent tumor biopsy, unless bone-only disease

4) Documented HER2-negative tumor based on local testing on most recent tumor biopsy (immunohistochemistry score 0/1+ or negative by in situ hybridization HER2/CP17 ratio < 2 or for single probe assessment HER2 copy number < 4)

5) Post-menopausal subjects considered to be in the post-menopausal state as defined by one of the following:

   a. Age ≥ 60 years

   b. Age < 60 years and cessation of regular menses for at least 12 consecutive months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and serum estradiol and follicle-stimulating hormone (FSH) level within the post-menopausal range

   c. Prior bilateral oophorectomy

   d. Pre-/peri-menopausal women can be enrolled if amenable to be treated with the luteinizing-hormone releasing hormone (LHRH) agonist, goserelin. Subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug. If subjects have received an alternative LHRH agonist prior to study entry, they must switch to goserelin on or before C1D1 for the duration of the study

6) Measurable disease defined per RECIST v. 1.1, or bone-only disease must have a lytic or mixed lytic blastic lesion that can be accurately assessed by computed tomography (CT) or magnetic resonance imaging (MRI). Subjects with bone-only disease and blastic-only metastases are not eligible

7) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study drug dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted])
8) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1
9) Life expectancy of ≥ 3 months, in the opinion of the investigator
10) Adequate organ function defined as follows:
    a. Hematologic: Platelets ≥ 100 x 10^9/L; Hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5 x 10^9/L (without platelet transfusion or any granulocytic growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)
    b. Hepatic: AST / ALT ≤ 2.5 x upper limit of normal (ULN) (if liver metastases are present, ≤ 5 x ULN); total or conjugated bilirubin ≤ 1.5 x ULN
    c. Renal: Serum Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 60 mL/min as calculated by the Cockroft-Gault method
11) Coagulation: International Normalized Ratio (INR) ≤ 1.2
12) Negative serum pregnancy test (Appendix 5)
13) Females who are nursing must agree to discontinue nursing before the first dose of GS-5829
14) Able and willing to provide written informed consent to participate in the study

Exclusion Criteria:

Subjects who meet any of the following exclusion criteria are not to be enrolled in this study:

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or the Gilead medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion
2) Known brain metastasis or leptomeningeal disease
3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to first dose of study drug, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

4) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of C1D1

5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (i.e., larger than what is required for placement of central venous access, percutaneous feeding tube) within 28 days of the first dose of study drug

6) Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of GS-5829, including any unresolved nausea, vomiting, or diarrhea that is Common Terminology Criteria for Adverse Events (CTCAE) Grade > 1

7) Minor surgical procedure(s) within 7 days of enrollment or randomization, or not yet recovered from prior surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment or randomization is acceptable)

8) History of a concurrent or second malignancy, except for: adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; adequately treated Stage 1 or 2 cancer currently in complete remission; any other cancer that has been in complete remission for ≥ 5 years

9) Anti-tumor therapy (chemotherapy, chemoradiation, radiation, antibody therapy, molecular targeted therapy) within 21 days of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); 5 half-lives of any investigational drug; concurrent use of goserelin for pre-/peri-menopausal breast cancer and exemestane or fulvestrant per the protocol are permitted.

10) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 470 ms). Subjects who screen fail due to this criterion are not eligible to be re-screened

11) Prior exposure to any bromodomain (BET) inhibitors or immunotherapy

12) Evidence of bleeding diathesis or clinically significant bleeding, within 28 days of C1D1 or history of hemoptysis of ≥ 2.5mL/1 teaspoon within 6 months of C1D1

13) Anticoagulation therapy within 7 days of C1D1, including acetylsalicylic acid, low molecular weight heparin, or warfarin.

14) Known human immunodeficiency virus (HIV) infection

15) Hepatitis B surface Antigen (HBsAg) positive

16) Hepatitis C virus (HCV) antibody positive with HCV RNA positive

17) Use of moderate/strong cytochrome P450 (CYP)3A4 inhibitors or moderate/strong CYP3A4 inducers within 2 weeks prior to the first dose of study drug

18) History of high grade esophageal or gastric varices

Study Procedures/ Frequency:

Screening:

Screening will commence with obtaining the subject's signed informed consent and will occur up to 28 days prior to the first dosing of study drug on C1D1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead electrocardiogram (ECG), echocardiogram (ECHO), ECOG Performance Status, prior/concomitant medication review, chemistry, hematology and coagulation, hepatitis B virus (HBV)/HCV testing, serum pregnancy β-HCG, serum estradiol and FSH for subjects < 60 years old and who have been amenorrheic for at least 12 consecutive months) and CT or MRI and bone scans. Scans that meet protocol requirements that are obtained as part of standard medical practice up to 28 days prior to C1D1 are acceptable as long as: (1) tests were performed using the method requirements outlined in RECIST v.1.1, (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given subject, and (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the subject's source notes. Baseline tumor lesions will be measured and characterized prior to C1D1 to assess the subject's disease status prior to beginning treatment

Treatment:

Phase 1b Dose Escalation with Exemestane or Fulvestrant

Subjects who meet eligibility criteria will receive GS-5829 orally once daily combined with either 25 mg of exemestane orally once daily or fulvestrant intramuscularly on Day 1, 15 (for whom C1D1 is the subject's first dose of fulvestrant), 29 and then every 28 days (± 3 days). Subjects in the Phase 1b Dose Escalation portion may initiate exemestane (Group A) or fulvestrant (Group B) any time prior to, or on, C1D1. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including an assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, GS-5829 PK, PD markers, and

	biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a CT scan (or MRI) scan every 8 weeks for the first year, then every 12 weeks. A subject who does not show evidence of disease progression may continue receiving GS-5829 once daily and exemestane (Group A) or fulvestrant (Group B) until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death whichever comes first. After discontinuation of study treatment, subjects will be followed for safety for 30 days and up to two years for OS. PK and PD samples for GS-5829 will be collected on Day 1 and Day 15 of Cycle 1 at pre-dose 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post-dose and anytime on Day 1 of Cycles 2 through 6. **Randomized Phase 2 Dose Expansion** Sparse PK and PD samples will be collected at pre-dose and anytime between 1 to 4 hours post-dose on Day 1 and Day 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 3 and 6. Note: PK samples will only be collected for subjects who are randomized to a GS-5829 combination arm.
Test Product, Dose, and Mode of Administration:	GS-5829 will be supplied as GS-5829-02 and is available as round, plain-faced tablets containing 1 mg or 5 mg GS-5829. GS-5829 tablets will be self-administered orally once daily, beginning on C1D1 of the study and thereafter at approximately the same time each day until end of treatment (EOT). For subjects in Group A, 25 mg exemestane tablets will be self-administered orally once daily (or in accordance with locally approved labeling), beginning on C1D1 of the study and thereafter at approximately the same time each day until the EOT. For subjects in Group B, fulvestrant will be administered intramuscularly (in accordance with locally approved labeling) by the clinic staff approximately every 28 days (± 3 days) until the EOT. For all subjects in the Phase 1b Dose Escalation or the Randomized Phase 2 Dose Expansion part of the study for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of fulvestrant will be administered on Cycle 1, Day 15 (± 3 days).

Reference Therapy, Dose, and Mode of Administration:	The reference therapy in the Randomized Phase 2 Dose Expansion portion of the study is exemestane alone and fulvestrant alone. For subjects in Group 1 of the Randomized Phase 2 Dose Expansion, exemestane 25 mg tablets will be self-administered orally once daily (or in accordance with locally approved labeling), beginning on C1D1 of the study and thereafter at approximately the same time each day until the EOT. For subjects in Group 2 of the Randomized Phase 2 Dose Expansion, fulvestrant will be administered intramuscularly (in accordance with locally approved labeling) by the clinic staff approximately every 28 days (±3 days) until the EOT. For all subjects in the dose expansion Phase and for subjects in the dose escalation phase for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of fulvestrant will be administered on Cycle 1 Day 15 (± 3 days).
Criteria for Evaluation:	**Phase 1b Dose Escalation and Randomized Phase 2 Dose Expansion**
Safety:	Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements, and the documentation of AEs
Efficacy:	PFS – defined as the interval from Day 1 to the earlier of the first documented confirmed disease progression or death from any cause ORR – defined as the proportion of subjects who achieve a CR or PR CBR - defined as the proportion of subjects who achieve a CR or PR or SD that lasts for ≥ 24 weeks OS - defined as interval from first dose date to date of death from any cause
Pharmacokinetics:	Phase 1b Dose Escalation: The PK parameters for GS-5829 will be calculated as applicable: [e.g. C_{max}, and AUC_{tau}]

Statistical Methods: Analysis Methods

Phase 1b Dose Escalation: The incidence of DLTs, AEs, serious adverse events (SAEs), and clinically significant laboratory abnormalities in subjects treated with GS-5829 in combination with exemestane or fulvestrant will be evaluated.

Randomized Phase 2 Dose Expansion: The Intent-to-Treat (ITT) analysis set includes all subjects who are randomized, regardless of whether subjects receive any study drug(s) or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization. The analysis of PFS based on the ITT analysis set will be considered the primary analysis of the study.

The Per-Protocol (PP) analysis set includes data from subjects in the ITT analysis set who meet the general criteria defining the target population for this study: those who are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Treatment assignment will be designated according to the actual treatment received. The PP analysis set will be used in sensitivity analyses of efficacy endpoints.

A Safety Analysis Set for this study consists of all subjects who receive ≥ 1 dose of study drug. Other analysis sets (DLT evaluable analysis set, PK analysis set, and biomarker analysis set) will be used for the corresponding analyses.

Subject characteristics and study results will be described and summarized by dose level and by study visit for the relevant analysis sets. Descriptive summaries will be prepared to show sample size, mean, standard deviation (StD), 90% confidence intervals (CIs) on the mean, median, minimum and maximum for continuous variables, and counts, percentages and 90% CIs on the percentage for categorical variables.

The log-rank test will be used for the analyses of PFS. Kaplan-Meier estimates and plots will be provided. ORR will be calculated along with the 95% CIs based on exact method and compared between treatment arms by Fisher's exact test. Based on the Safety Analysis Set, information regarding study drug administration, study drug compliance and safety variables will be described and summarized.

Using data from the relevant Analysis Sets, GS-5829 plasma concentrations and whole blood. PD markers will also be described and summarized. Plasma concentrations of GS-5829 metabolite(s), fulvestrant and/or exemestane may also be determined and PK explored.

Sample Size

Up to approximate 60 subjects will be enrolled in the Phase1b Dose Escalation portion of the study.

Total enrollment will be 120 subjects approximately in Randomized Phase 2 Dose Expansion portion. In Group 1 of the Randomized Phase 2 Dose Expansion portion of the study, approximately 60 subjects will be randomized to receive GS-5829 in combination with exemestane or exemestane alone in a 2:1 ratio. Similarly, in Group 2 of the Randomized Phase 2 Dose Expansion portion of the study, approximately 60 subjects will be randomized to receive GS-5829 in combination with fulvestrant or fulvestrant alone in a 2:1 ratio. The sample size of 60 subjects in each group (40 in the combination arm and 20 in the exemestane alone or fulvestrant alone arm) will provide 37 events in total and greater than 80% power to detect the difference in PFS between GS-5829 in combination with exemestane and exemestane alone and between GS-5829 in combination with fulvestrant and fulvestrant alone with 0.1 two-sided significance level, assuming a median PFS of 5 months for subjects who receive exemestane alone or fulvestrant alone, a median PFS of 12.5 months in subjects who receive GS-5829 in combination with exemestane or fulvestrant, accrual period of 6 months and total study duration of 18 months and a drop-out rate of 10% by 12 months.

An interim analysis may be performed separately when 22 events have been reached in each group. The purpose of this analysis is to have an early evaluation of the safety and efficacy of GS-5829 in combination with exemestane or fulvestrant. The interim analysis will assess either an expansion or study stop on any one of the arms independent of one another. The trial will continue after the interim analysis.

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents.

GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate transaminase
AUC_{tau}	area under the plasma concentration-time curve
BCRP	breast cancer resistance protein
BET	bromodomain and extra-terminal
BRD	bromodomain
CBC	complete blood count
CBR	Clinical benefit rate
C_{max}	maximum concentration observed
C_{tau}	concentration at the end of the dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRPC	castrate-resistant prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DSPH	Drug Safety and Public Health
ECHO	echocardiogram
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
ER	estrogen receptor
eSAE	electronic serious adverse events
FAS	full analysis set
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone

GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HNSTD	highest non-severely toxic dose
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
IxRS	Interactive voice/web Response System
LHRH	luteinizing-hormone releasing hormone
mCRPC	metastatic castrate-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MYC	myelocytomatosis viral oncogene homolog
NCI	National Cancer Institute
ORR	overall response rate
OS	overall survival
PD	pharmacodynamics
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
QD	every day
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNAPII	RNA polymerase II
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	stable disease
StD	standard deviation
SOC	system organ class
SOP	standard operating procedure
SRT	safety review team
STD	severely toxic dose
SUSAR	suspected unexpected serious adverse reactions

$t_{1/2}$	terminal phase half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WBC	white blood cell

1. INTRODUCTION

1.1. Background

GS-5829 is a small-molecule inhibitor of the highly conserved bromodomain pockets of the bromodomain and extraterminal (BET) proteins. Bromodomain and extraterminal proteins regulate specific gene expression by enhancing ribonucleic acid (RNA) polymerase II (RNAPII)mediated transcription. Signal transduction pathways recruit BET proteins to target genes through posttranslational modification of histone proteins in the form of lysine acetylation {Belkina et al 2012, Hargreaves et al 2009}. The tandem bromodomain motifs of BET proteins specifically recognize acetylated histones and, in turn, recruit protein factors that regulate RNAPII {Shi et al 2014}. The BET family includes bromodomain-containing proteins 2, 3, 4, and T (BRD2, 3, 4, and T). BRD2, 3 and 4 are widely expressed and regulate gene transcription in diverse cell types, including malignant cells, whereas BRDT expression is restricted to the testes.

BRD2, 3, 4 are essential regulators of the expression or activity of several key oncogenic transcription factors, including v-myc avian myelocytomatosis viral oncogene homolog (MYC) and the androgen receptor (AR) {Shi et al 2014}. Transcription of the MYC gene is dependent on BET proteins in many cells {Mertz et al 2011}. Androgen receptor-dependent transcription of target genes requires BET proteins in prostate cancer cells {Asangani et al 2014}. Cancer cells addicted to MYC and AR are highly sensitive to BET protein inhibition {Asangani et al 2014, Delmore et al 2011, Mertz et al 2011}, which provides the basic therapeutic rationale for BET inhibition with GS-5829 for the treatment of cancer.

MYC promotes cell proliferation, cell survival, and metabolic adaptation and is frequently overexpressed in human cancers {Dang 2012}. Data generated at Gilead demonstrated MYC overexpression to be prevalent in 76% of prostate cancer (n = 60), 67% of diffuse large B-cell lymphoma (DLBCL) (n = 98), 65% of multiple myeloma (MM, n=30), 73% of colorectal cancer (n = 60), and 80% of ovarian cancer (n = 60) cases examined (PC-350-2083). These data are consistent with literature that reports a high incidence of MYC expression in these and other cancers {Affer et al 2014, Barrans et al 2010, Chesi et al 2008, Chng et al 2011, Glitza et al 2014, Hawksworth et al 2010, Nesbit et al 1999, Nupponen et al 1998, Perry et al 2014}. The AR is a nuclear hormone receptor that is nearly ubiquitously expressed in prostate cancer (PC-350-2083) and activates growth and survival signals both by binding to androgen, its natural ligand, and through androgen-independent mechanisms {Yuan et al 2014}.

A number of orally administered, BET-directed compounds (TEN-010, CPI-0610, OTX015, ZEN-3365, and GSK525762) are currently in early-stage clinical development for the treatment of solid tumors or hematologic cancers. Initial evidence of clinical activity at tolerated doses has been reported for the BET inhibitor OTX015 in subjects with refractory hematological cancers {Herait et al 2014}. GS-5829 is an orally available small-molecule inhibitor of BET proteins that is being developed by Gilead Sciences, Inc. for the treatment of solid tumors, including castrate-resistant prostate cancer (CRPC), and hematologic malignancies. In nonclinical studies, GS-5829 inhibited cell growth and induced apoptosis of solid tumor and hematological cancer

cells by inhibiting BET protein-dependent transcription of MYC and other oncogenic pathways, including transcription mediated by the AR in prostate cancer cells.

1.2. GS-5829

1.2.1. General Information

For further information on the GS-5829, refer to the current investigator's brochure for GS-5829.

1.2.2. Preclinical Pharmacology and Toxicology

1.2.2.1. Absorption, Distribution, Metabolism, and Elimination

GS-5829 shows moderate plasma protein binding and volumes of distribution in nonclinical species that are similar to or slightly higher than total body water. Systemic clearance in nonclinical species is generally well predicted from the rates of metabolism by hepatocytes. Since GS-5829 has high metabolic stability with human hepatic material in vitro, it is likely to show low clearance in humans. The major route of metabolism of GS-5829 involves hydroxylation of the 5-methyl moiety on the 3,4-dimethly isoxazole ring catalyzed primarily by CYP3A4 and CYP3A5 enzymes in humans.

Consistent with the moderate to high bioavailability seen in nonclinical species, GS-5829 shows high forward permeability across Caco-2 monolayers, and low efflux, but GS-5829 is a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

GS-5829 has relatively high unbound fraction in cell culture medium containing fetal bovine serum. Competitive dialysis between cell culture median and human, dog and mouse plasma yielded a ratio of unbound fractions of 5.7, 15.2 and 13.2 respectively.

GS-5829 is unlikely to cause clinical interaction through inhibition of CYP1A2, CYP2C9, CYP2C19, or CYP2D6, CYP2B6, CYP2C8, CYP3A or UGT1A1, so the potential for causing drug interactions through inhibition of those enzymes is low. GS-5829 is also a weak inhibitor of the human efflux transporters, P-gp and BCRP, and the uptake transporters, OATP1B1 and OATP1B3.

1.2.2.2. Nonclinical Toxicology

Nonclinical safety pharmacology and toxicology studies have characterized the safety of GS-5829 through single and repeat dose toxicology studies. All pivotal toxicology studies were conducted in full compliance with Good Laboratory Practice regulations (21 CFR 58). The scope of the nonclinical safety evaluation is consistent with the guidance issued by the International Conference on Harmonisation (ICH).

In nonclinical pharmacology studies, GS-5829 showed no significant adverse effects on central nervous, respiratory or cardiovascular system functioning at the projected exposure and human target dose of 25 mg once daily.

The following target organs/systems were identified in the nonclinical toxicology studies: hematopoietic and male reproductive system (mice and dogs), the adrenal and skin (mice), and the gastrointestinal tract, respiratory and cardiac (dogs). With the exception of the adrenals in the mouse and the respiratory and cardiac hemorrhages observed in dogs, target organs are as expected based on the known pharmacology of GS-5829. The dog was the more sensitive species, with the no-observed-adverse-effect levels in the mouse and dog being 10 and 0.03 mg/kg/day respectively. The severely toxic dose in 10% of mice and the highest non-severely toxic dose (HNSTD) in dogs were 25 and 0.1 mg/kg/day, respectively.

Hematopoietic effects include decreases in white blood cells (WBC), lymphocytes, platelets and reticulocyte counts as well as mild reduced cellularity in the marrow in mice at doses of ≥ 10 mg/kg/day. Minimal to marked decrease in bone marrow cellularity, decrease in lymphocytes in the lymphoid tissues (spleen, thymus, lymph nodes and gastrointestinal associated lymphoid tissue), decrease in neutrophils and platelets were observed at 0.3 mg/kg/day in dogs. Elevated fibrinogen was also noted at 0.3 mg/kg/day in dogs.

Mild to moderate alveolar (lung) hemorrhage was observed at ≥ 0.1 mg/kg/day in dogs. Mild hemorrhage in the left atrioventricular valve of the heart was seen at 0.3 mg/kg/day in 1 of 6 dogs. The mechanism for the hemorrhage is not known. Prothrombin time and partial thromboplastin time measurements were normal. The anatomic pattern of the hemorrhage in the lung field and microscopy was considered potentially consistent with pneumonia, however bacteria were not identified.

In the male reproductive system, decreased testes weight with oligospermia/aspermia were observed in both mouse and dog studies at 25 and 0.3 mg/kg/day respectively. Minimal to moderate vacuolation of the seminiferous tubules occurred at ≥ 0.1 mg/kg/day in the dog. These changes are consistent with the known effects of a bromodomain inhibitor on the testes.

The gastrointestinal findings in the dog included minimal to mild mucosal atrophy, mucosal hemorrhage and crypt hyperplasia in the stomach or intestines at ≥ 0.1 mg/kg/day. Adrenal gland weight decreases were noted at 25 mg/kg/day and cytoplasmic vacuolation at ≥ 10 mg/kg/day in the mouse studies, of unknown cause. QT prolongation is not expected based on hERG, rodent and dog studies.

1.2.3. Clinical Trials of GS-5829

As of 02 June 2016, two clinical studies evaluating GS-5829 have been initiated. One study (GS-US-350-1599) includes subjects with advanced solid tumors, ER+Her2- breast cancer, and lymphomas. This study is an ongoing open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, pharmacokinetics (PK), and PD of GS-5829 in subjects with advanced solid tumors and lymphomas. This study includes a cohort of subjects with advanced stage breast cancer will receive GS-5829 combined with exemestane and fulvestrant. Doses planned for this study are 0.6, 1.4, 2, 3, 4, 6, 9, and 12 mg once daily. Pharmacokinetic data are available from 3 dose levels of the single agent GS-5829 in Study GS-US-350-1599 (0.6, 1.4, 2 mg, and 3mg once daily). GS-5829 is well-absorbed with higher than predicted plasma exposures in humans. No clinically detectable trend in laboratory abnormalities in relationship to

dose has been observed. A Grade 3 thrombocytopenia that was considered as DLT was observed in 1 of 6 subjects at 3.0 mg.

A second clinical study (GS-US-350-1604) in subjects with metastatic castrate-resistant prostate cancer (mCRPC) has completed the first cohort enrollment with 4 evaluable subjects at the 2 mg single agent dose of GS-5829. No DLTs has been reported as of 2 June 2016. This study is an open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, and PD of GS-5829 as a single agent and combined with enzalutamide in subjects with mCRPC. Doses planned for this study are 1.4, 2, 3, 4, 6, and 9 mg once daily.

Please refer to the current GS-5829 investigator's brochure for additional details.

1.2.4. Information about Exemestane

Exemestane is an irreversible, steroidal aromatase inactivator, structurally related to the natural substrate androstenedione. It acts as a false substrate for the aromatase enzyme and is processed to an intermediate that binds irreversibly to the active site of the enzyme, causing its inactivation, an effect also known as "suicide inhibition." Exemestane significantly lowers circulating estrogen concentrations in post-menopausal women. In the US, exemestane is approved for the treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy. For current information about exemestane (Aromasin ®) refer to the regional prescribing information (Appendix 8 or the summary of product characteristics in the pharmacy binder.

1.2.5. Information about Fulvestrant

Fulvestrant is an estrogen receptor antagonist that binds to the estrogen receptor in a competitive manner with affinity comparable to that of estradiol and down-regulates the ER protein in human breast cancer cells. In vitro studies demonstrated that fulvestrant is a reversible inhibitor of the growth of tamoxifen resistant as well as estrogen sensitive human breast cancer cell lines. In vivo tumor studies fulvestrant delayed the establishment of tumors from xenografts of human breast cancer MCF-7 cells in nude mice. Fulvestrant inhibited the growth of established MCF7 xenografts and of tamoxifen resistant breast tumor xenografts. In the US, fulvestrant is approved for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following anti-estrogen therapy. For current information about fulvestrant (Faslodex®), refer to Appendix 9 or the summary of product characteristics in the pharmacy binder.

1.3. Rationale for This Study

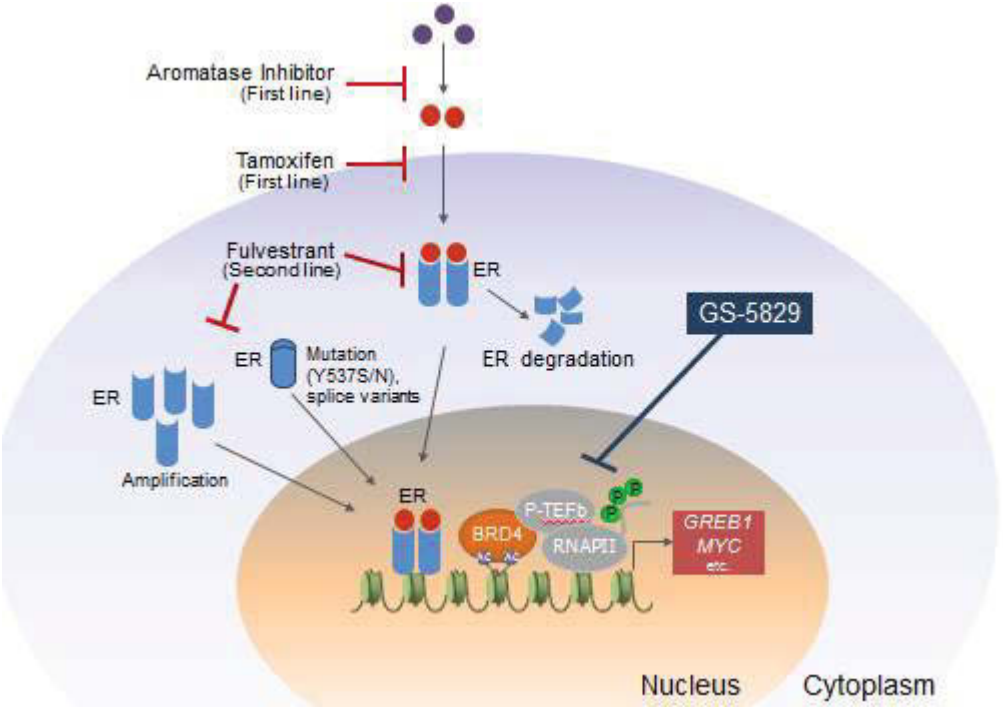
Approximately 75% of breast cancers express the estrogen receptor (ER), a nuclear hormone receptor and transcription factor that promotes the expression of genes involved in cell growth and survival {Clark et al 1984}. Anti-estrogen endocrine therapies, such as aromatase inhibitors (AIs) and tamoxifen, are the primary treatments for early stage ER-positive breast cancers but many women relapse during or after completing these adjuvant hormonal therapies. In the metastatic setting, single-agent treatment with AIs, tamoxifen, or the selective ER degrader,

fulvestrant, has limited benefit. When combined with other targeted therapies such as the Cyclin-Dependent Kinase (CDK) 4/6 inhibitor, palbociclib, the benefit of first-line antiestrogen therapy significantly improves PFS. Standard of care includes sequential administration of endocrine therapies until hormone resistance occurs, at which time patients are usually transitioned to chemotherapy and eventually die. Therefore, the development of effective therapies that improve response to endocrine therapy and prevent or reverse resistance continues to be of clinical importance.

Resistance to endocrine therapy is mediated by several mechanisms that enable reactivation of ER-driven transcription under conditions of low estrogen (i.e. estrogen-independent transcription by the ER). These mechanisms include ER overexpression, activating ER mutations, increased expression of ER co-activators, or increased expression of ER-target genes such as MYC and cyclin D1 {Osborne et al 2011}. Importantly, BET proteins are required for both estrogen-dependent and estrogen-independent transcription by the ER receptor. BRD4 and BRD3 are recruited to ER target genes, including MYC, where they promote transcription by RNA polymerase II. In preclinical studies, the BET inhibitor, JQ1, decreased ER-mediated gene transcription and inhibited the growth of ER-positive tumors {Nagarajan et al 2014, Sengupta et al 2015}. In addition, combination of JQ1 with fulvestrant significantly increased time to disease progression in an endocrine-resistant ER-positive xenograft mouse breast tumor {Feng et al 2014}.

The combination of GS-5829 and an anti-estrogen such as fulvestrant or an AI such as exemestane may increase the efficacy of endocrine therapy in patients with advanced ER-positive breast cancer by targeting orthogonal mechanisms. The combination is expected to lead to overall greater inhibition of ER-dependent transcription by blocking distinct aspects of ER signaling (reduced ligand-dependent ER activation with AI, reduced ER protein stability with fulvestrant, and reduced BET-dependent transcription of ER target genes with GS-5829). By directly inhibiting the transcription of ER target genes such as MYC, GS-5829 is hypothesized to block established mechanisms of resistance to endocrine therapy. BET proteins also promote transcription of several ER-independent cell cycle genes, including CDK 6, which may additionally contribute to the combination activity in ER+ breast cancer cells. Preliminary Gilead data has demonstrated a synergistic effect of fulvestrant and GS-5829 to inhibit growth of ER-positive breast cancer cell lines in vitro and to inhibit growth of patient-derived ER-positive breast cancer xenografts in mice.

Figure 1-1. Mechanism of Action of GS-5829 to Reduce Transcription of ER Target Genes in Cancer Cells



Overall, the pre-clinical studies demonstrate that GS-5829 is a potent and selective inhibitor of BET proteins and support the use of GS-5829 to treat solid tumors and hematological cancers.

1.3.1. Rationale for Dose Selection

GS-5829 is being evaluated in two ongoing studies: 1) GS-US-350-1599, a Phase 1 study to evaluate safety and tolerability in subjects with advanced stage solid tumors and lymphoma, and 2) GS-US-350-1604, a Phase 1b/2 study to evaluate safety and tolerability in subjects with castrate-resistant prostate cancer either as single agent or in combination with enzalutamide. As of June 2nd 2016, a total of five subjects have been dosed with single agent GS-5829 at 2 mg once daily, seven subjects at 3mg once daily, and no DLTs have been reported. No drug interactions or overlapping toxicities are expected between GS-5829 and exemestane or fulvestrant. Based on a dose limiting toxicity (DLT) model (Bayesian logistic regression model, refer to Appendix 10) utilizing GS-5829 safety data from different dose levels collected so far, the probabilities of underdosing (DLT rate<16%) (see Appendix 10 for results), falling in the target interval of DLT rate (between 16% and 33%) and overdosing (DLT rate>33%) will be about 44%, 51% and 5%, respectively, if the next cohort is at 3.0 mg. The probabilities of underdosing, falling in the target interval of DLT rate and overdosing will be about 87%, 12%, and 1%, respectively, if the next cohort is at 2.0 mg. Because there is a high (87%) chance of underdosing at 2mg and a low (5%) chance of overdosing at 3mg, the starting dose of GS-5829 is planned as 3 mg for both Groups A and B in the Phase 1b Dose Escalation portion of this study. The starting dose level may be either higher or lower than 3 mg once daily, if either a

higher or lower dose has been demonstrated to be both safe and tolerable in Studies GS-US-350-1599 and GS-US-250-1604, the new dose level will be selected prior to initiating dosing in this study.

The recommended dose of GS-5829 to be combined with exemestane or fulvestrant in the Randomized Phase 2 Dose Expansion part of this study will not exceed the maximum tolerated dose (MTD) identified by either Phase 1b dose escalation from this study or from GS-US-350-1599, whichever dose is higher. A lower dose may be chosen for the Randomized Phase 2 Dose Expansion study based on emerging safety, PK, pharmacodynamics (PD), and efficacy results from this study and including additional safety data generated from other ongoing Phase 1 and 2 studies with GS-5829.

1.4. Risk/Benefit Assessment for the Study

Based on the systemic concentrations of GS-5829 measured in the repeat dose toxicity studies in mice and dogs, the margins of exposure at the severely toxic dose in 10% of rodents (STD10) in mice and HNSTD in dog are approximately 6.3- and 1-fold, respectively, at the anticipated clinically efficacious exposure. Another bromodomain inhibitor in development has identified thrombocytopenia as the earliest signs of toxicity in human studies, a toxicity which may be easily monitored.

As of 2 June 2016, the 2 mg has been cleared as single agent dosing in the First-In-Human study GS-US-350-1599 and prostate cancer study GS-US-350-1604 respectively. In addition, to minimize the risk of excessive toxicity, the dose escalation of GS-5829 in this protocol will not increase at > 50% at each subsequent dose level.

Assessments for AEs and monitoring for laboratory abnormalities are specified in the protocol and include symptom and AE assessment on Days 1, 8, 15, 22 of the first 28 day cycle and then every 28 days, until end of treatment (EOT) followed by a 30-day Safety Follow-Up Visit. Physical examinations will occur on Day 1of each 28-day cycle, until EOT followed by a 30-day Safety Follow-Up Visit.

The safety monitoring frequency is considered sufficient to identify potential AEs as they emerge. In addition, mitigation strategies are incorporated into the study design. The inclusion and exclusion criteria are designed to ensure subjects have acceptable organ function to be eligible for this study, such that confounding significant co-morbidities are excluded. Study medications will continue until disease progression, unacceptable toxicity, consent withdrawal, or subject's refusal of treatment.

Exemestane and fulvestrant have been approved for treatment of advanced breast cancer in postmenopausal women whose disease has progressed either following tamoxifen or anti-estrogen therapy. The known toxicities for exemestane for this patient population are hot flushes, nausea, fatigue, increase sweating, increased appetite (Appendix 8). The know toxicities for fulvestrant are increased hepatic enzymes (ALT, AST and ALP), injection side pain, nausea, bone pain, arthralgia, headache, back pain, fatigue, pain in extremity, hot flash, vomiting, anorexia, asthenia, musculoskeletal pain, cough, dyspnea and constipation (Appendix 9).

1.5. Potential Benefits

The combination of GS-5829 with exemestane and fulvestrant is expected to lead to overall greater inhibition of ER-dependent transcription by blocking distinct aspects of ER signaling (reduced ligand-dependent ER activation with AI such as exemestane, reduced ER protein stability with fulvestrant, and reduced BET-dependent transcription of ER target genes with GS-5829). By directly inhibiting the transcription of ER target genes such as MYC, GS-5829 is hypothesized to block established mechanisms of resistance to endocrine therapy. BET proteins also promote transcription of several ER-independent cell cycle genes, including CDK 6, which may additionally contribute to the combination activity in ER+ breast cancer cells.

1.6. Compliance

This study will be conducted in compliance with this protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

2. OBJECTIVES

The primary objectives:

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive Her2-negative breast cancer (ER+/HER2- BrCa)

- To determine the MTD if not already determined from GS-US-350-1599, or the recommended Phase 2 dose (RP2D) of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa.

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa, as measured by PFS

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by PFS

The secondary objectives:

Phase 1b Dose Escalation

- To evaluate the PK of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa, as measured by overall response rate (ORR) and clinical benefit rate (CBR) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1. ORR is defined as the proportion of subjects with response (complete response [CR], or partial response [PR]). CBR is defined as the proportion of subjects with CR, PR, or stable disease (SD) that lasts for $\geq$ 24 weeks

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by ORR or CBR

- To evaluate the safety and tolerability of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa

- To evaluate the safety and tolerability of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa

- To evaluate the overall survival (OS) for subjects with advanced ER+/HER2-BrCa who receive GS-5829 in combination with exemestane or fulvestrant comparing to exemestane or fulvestrant alone

The exploratory objectives:

PPD

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.

3.2. Study Design

Phase 1b Dose Escalation:

Cohorts of postmenopausal women with (ER+/HER2- BrCa), for whom no standard curative therapy exists and who are candidates for exemestane or fulvestrant, will be sequentially enrolled at progressively higher dose levels of oral GS-5829 in combination with standard doses of exemestane or fulvestrant. Up to 60 subjects will be enrolled in the Phase 1b Dose Escalation portion of the study. The starting dose of GS-5829 will be the either 3.0 mg once daily or a dose level that has been demonstrated to be safe and tolerable based on other ongoing studies (GS-US-350-1599, GS-US-350-1604).

Eligible subjects will be assigned to either Group A or Group B based on prior treatment and the investigators' decision. Group A will initiate with GS-5829 orally once daily on Cycle 1 Day 1 (C1D1) combined with 25 mg of exemestane administered orally once daily (or in accordance with locally approved labeling). The subject may initiate exemestane any time prior to, or on, C1D1. Group B will initiate GS-5829 orally once daily on C1D1 with fulvestrant administered intramuscularly every 28 days (± 3 days) (or in accordance with locally approved labeling). The subject may initiate fulvestrant any time prior to, or on, C1D1. If C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of fulvestrant should be administered on Cycle 1 Day 15.

The doses of GS-5829 for each Dose Level are shown in the following table.

Table 3-1. Phase 1b Dose Escalation: Combination of GS-5829 with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

Dose Level	GS-5829 (once daily)	Group A Exemestane	Group B Fulvestrant**
1*	3 mg	25 mg orally once daily (or in accordance with locally approved labeling)	500 mg intramuscularly day 1, 29 and then every 28 days (or in accordance with locally approved labeling)
2	4 mg		
3	6 mg		
4	9 mg		

* The initial dose level may be higher (4 mg) or lower (2 mg) than Dose Level 1, depending on results from ongoing studies and emerging PK data.

** Subjects initiating fulvestrant on this study on C1D1 and not having received any prior dose of fulvestrant should receive a single additional dose of fulvestrant on Cycle 1 Day 15.

Group A and Group B will dose escalate independently of each other; each cohort will consist of 3 newly enrolled subjects who will be treated at the specified dose level. Dose escalation will continue until identification of the MTD of GS-5829, or until a RP2D is reached.

After all the subjects in each cohort have been followed for at least 28 days after the first dose of GS-5829, a DLT model (Bayesian logistic regression model, see Appendix 10) utilizing all available GS-5829 safety data will be built and will provide estimates of DLT rates at all dose levels. The recommended dose from the dose-DLT model for the next cohort will have the highest probability that the DLT rate will fall in the target interval (16%, 33%), and a probability of < 25% that the DLT rate exceeds 33%.

The dose escalation decision and the final decision for the RP2D will be made by the Safety Review Team (SRT), following a review of the model recommendation and all relevant data including safety information, PK, biomarkers, clinical data from evaluable subjects.

The SRT will consist of at least one investigator and the following Gilead Sciences, Inc. (Gilead) study team members: the Gilead medical monitor, representatives from Drug Safety and Public Health (DSPH) and Biostatistics. Others may be invited to participate as members of the SRT if additional expertise is desired. The Gilead medical monitor serves as the chair of the SRT.

The recommended dose of GS-5829 to be combined with exemestane or fulvestrant in the Randomized Phase 2 Dose Expansion part of this study will be determined based on the data available in the Phase 1b Dose Escalation portion of this study and from studies GS-US-350-1599 and GS-US-350-1604. The recommended dose will not exceed the MTD identified by either the Phase 1b dose escalation from this study or from studies GS-US-350-1599 and 1604, whichever dose is higher. At least 6 subjects should have already been treated and evaluated at that dose level prior to enrolling subjects in the Randomized Phase 2 Dose Expansion.

Dose Limiting Toxicity (DLT) Definition

A DLT is a toxicity defined below and considered possibly related to GS-5829 if occurring during the DLT assessment window (Day 1 through Day 28) in each combination therapy cohort:

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3)
- Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour)
- Grade ≥ 4 thrombocytopenia (platelet count < 25,000/µL)
- Grade ≥ 3 thrombocytopenia (platelet count <50,000/µL but >25,000/µL) lasting > 7 days despite GS-5829 drug interruption
- Grade ≥ 2 bleeding (e.g. gastrointestinal, respiratory, epistaxis, purpura)

- Grade ≥ 3 or higher non-hematologic toxicity, except:

  — Grade 3 nausea or emesis with maximum duration of 48 hours on adequate medical therapy

  — Grade 3 diarrhea which persists for < 72 hours in the absence of maximal medical therapy

- Grade ≥ 2 non-hematologic treatment-emergent adverse event (TEAE) that in the opinion of the investigator is of potential clinical significance such that further dose escalation would expose subjects to unacceptable risk

- Treatment interruption of ≥ 7 days due to unresolved toxicity

For certain toxicities, such as laboratory assessments without a clear clinical correlate, a discussion between the investigator and the Gilead medical monitor may take place to determine if this AE should be assessed as a DLT. However, any Grade 3 or Grade 4 elevation in aspartate transaminase (AST) or alanine transaminase (ALT) associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug will be considered a DLT. See Section 3.2 for details.

Randomized Phase 2 Dose Expansion:

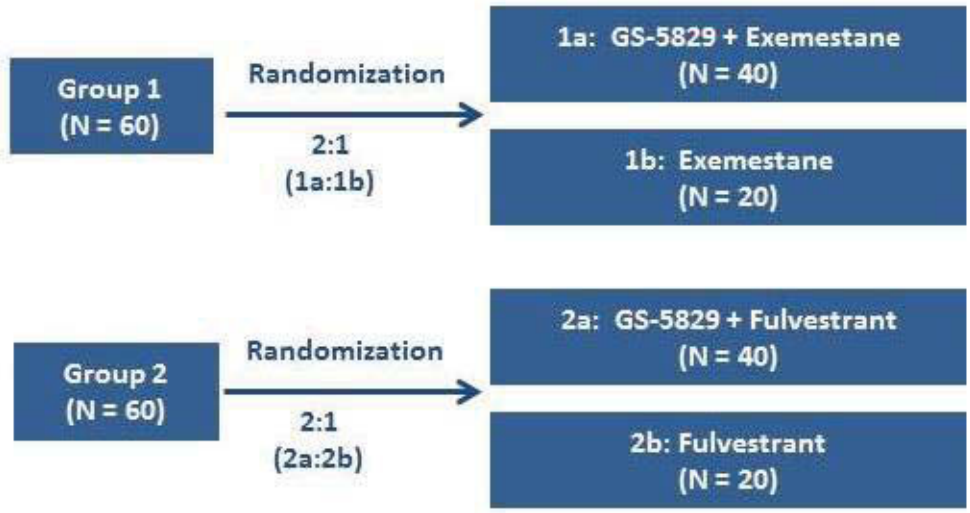
Approximately 120 female subjects who are post-menopausal with ER+/HER2- BrCa and who have had disease progression following anti-estrogen therapy will be enrolled.

- Approximately 60 subjects who have not previously received exemestane will be randomized in a 2:1 ratio to receive exemestane + GS-5829 or exemestane alone in Group 1.

- Approximately 60 subjects who have not previously received fulvestrant will be randomized in a 2:1 ratio to receive fulvestrant + GS-5829 or fulvestrant alone in Group 2.

GS-5829 and the anti-estrogen therapy (exemestane for Group 1 or fulvestrant for Group 2) will be initiated on C1D1.

Figure 3-1. Randomized Phase 2 Dose Expansion



3.3. Study Treatments

Subjects who meet eligibility criteria will receive GS-5829 orally once daily combined with either 25 mg of exemestane orally once daily or fulvestrant intramuscularly on Day 1, 15 (for whom C1D1 is the subject's first dose of fulvestrant), 29 and then every 28 days (± 3 days). Subjects in the Phase 1b Dose Escalation portion may initiate exemestane (Group A) or fulvestrant (Group B) any time prior to, or on, C1D1. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including an assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, GS-5829 PK, PD markers, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a CT scan (or MRI) scan every 8 weeks for the first year, then every 12 weeks.

Subjects who do not show evidence of disease progression may continue receiving GS-5829 combined with either exemestane (Group A) or fulvestrant (Group B) until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or death, whichever comes first.

Following treatment discontinuation, subjects will be followed for safety for 30 days and up to two years for OS.

3.4. Duration of Treatment

Subjects may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent or death, whichever comes first. See Section 3.5 for criteria for study drug discontinuation.

3.5. Criteria for Discontinuation of Study Drug

Study medication may be discontinued in the following instances:

- Documented progression of malignant disease
- Death
- Investigator discretion
- Non-compliance with study drug
- Subject decision
- Lost to follow-up
- Study termination by the sponsor
- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

3.6. Criteria for Removal from Study

Subjects may be removed from the study for the following reasons:

- Documented progression of malignant disease
- Death
- Investigator discretion
- Withdrawal of consent
- Lost to follow-up
- Study termination by the sponsor

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree

- Unacceptable toxicity, as defined in the toxicity management section of the protocol (Section 7), or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 60 subjects who meet the eligibility criteria will be enrolled in the Phase 1b Dose Escalation portion of the study.

Up to 120 subjects who meet the eligibility criteria will be enrolled in the Randomized Phase 2 Dose Expansion portion of the study.

4.2. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1) ≥18 years of age, female

2) Histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced disease not amenable to resection or radiation therapy with curative intent and who have progressed during treatment with at least one prior hormonal therapy. **Note:** In referring to prior hormonal therapy; targeted therapies, such as palbociclib and/or everolimus or investigative targeted therapies which were administered as part of a prior hormonal therapy regimen are allowed after the washout period has been reached.

    a. Phase 1b Dose Escalation - Subjects may have had unlimited prior hormonal therapy and a total of 2 prior chemotherapy regimens (adjuvant chemotherapy is considered 1 regimen). Subjects may have progressed on fulvestrant or exemestane as a single agent.

    b. Randomized Phase 2 Dose Expansion - Subjects may have had unlimited prior hormonal therapy, only one adjuvant chemotherapy is permitted (no prior chemotherapy for metastatic disease is allowed). Subject enrolling in Group 1 must be exemestane naïve and subjects enrolling in Group 2 must be fulvestrant naïve. If a subject is naïve to both exemestane and fulvestrant, it is the investigator's decision for which Group to enroll.

3) Documentation of ER positive (≥ 1% positive stained cells by local standards) based on the most recent tumor biopsy, unless bone-only disease

4) Documented HER2-negative tumor based on local testing on most recent tumor biopsy (immunohistochemistry score 0/1+ or negative by in situ hybridization HER2/CP17 ratio < 2 or for single probe assessment HER2 copy number < 4)

5) Post -menopausal subjects considered to be in the post-menopausal state as defined by one of the following:

    a. Age ≥ 60 years

b. Age < 60 years and cessation of regular menses for at least 12 consecutive months in the absence of chemotherapy, tamoxifen, toremifene, or ovarian suppression and serum estradiol and Follicle-stimulating hormone (FSH) level within the post-menopausal range

c. Prior bilateral oophorectomy

d. Pre-/peri-menopausal women can be enrolled if amenable to be treated with the luteinizing-hormone releasing hormone (LHRH) agonist goserelin. Subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug. If subjects have received an alternative LHRH agonist prior to study entry, they must switch to goserelin on or before C1D1 for the duration of the study

6) Measurable disease defined per RECIST v. 1.1 or bone-only disease must have a lytic or mixed lytic blastic lesion that can be accurately assessed by CT or MRI. Subjects with bone-only disease and blastic-only metastases are not eligible

7) All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study drug dosing (with the exception of alopecia [Grade 1 or 2 permitted] and neurotoxicity [Grade 1 or 2 permitted])

8) Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1

9) Life expectancy of ≥ 3 months, in the opinion of the investigator

10) Adequate organ function defined as follows:

a. Hematologic: Platelets ≥ 100 x 10^9/L; Hemoglobin ≥ 9.0 g/dL; ANC ≥ 1.5 x 10^9/L (without platelet transfusion or any granulocytic growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit)

b. Hepatic: AST / ALT ≤ 2.5 x upper limit of normal (ULN) (if liver metastases are present, ≤ 5 x ULN); total or conjugated bilirubin ≤ 1.5 x ULN

c. Renal: Serum Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 60 mL/min as calculated by the Cockroft-Gault method

11) Coagulation: International Normalized Ratio (INR) ≤ 1.2

12) Negative serum pregnancy test (Appendix 5)

13) Females who are nursing must agree to discontinue nursing before the first dose of GS-5829

14) Able and willing to provide written informed consent to participate in the study

4.3. Exclusion Criteria

Subjects who meet *any* of the following exclusion criteria are not to be enrolled in this study:

1) History or evidence of clinically significant disorder, condition, or disease that, in the opinion of the investigator or the Gilead medical monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

2) Known brain metastasis or leptomeningeal disease

3) Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, active or chronic bleeding event within 28 days prior to first dose of study drug, uncontrolled cardiac arrhythmia, or psychiatric illness/social situation that would limit compliance with study requirements as judged by treating physician

4) Myocardial infarction, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or serious uncontrolled cardiac arrhythmia within the last 6 months of C1D1

5) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (i.e., larger than what is required for placement of central venous access, percutaneous feeding tube) within 28 days of the first dose of study drug

6) Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of GS-5829, including any unresolved nausea, vomiting, or diarrhea that is CTCAE Grade > 1

7) Minor surgical procedure(s) within 7 days of enrollment or randomization, or not yet recovered from prior surgery (placement of central venous access device, fine needle aspiration, or endoscopic biliary stent ≥ 1 day before enrollment or randomization is acceptable)

8) History of a concurrent or second malignancy, except for: adequately treated local basal cell or squamous cell carcinoma of the skin; cervical carcinoma in situ; superficial bladder cancer; adequately treated Stage 1 or 2 cancer currently in complete remission; any other cancer that has been in complete remission for ≥ 5 years

9) Anti-tumor therapy (chemotherapy, chemoradiation, radiation, antibody therapy, molecular targeted therapy) within 21 days of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with t1/2 > 10 days); 5 half-lives of any investigational drug; concurrent use of goserelin for pre-/peri-menopausal breast cancer and exemestane or fulvestrant per the protocol are permitted.

10) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 470 ms). Subjects who screen fail due to this criterion are not eligible to be re-screened

11) Prior exposure to any bromodomain (BET) inhibitors or immunotherapy

12) Evidence of bleeding diathesis or clinically significant bleeding, within 28 days of C1D1 or history of hemoptysis of > 2.5mL/1 teaspoon within 6 months of C1D1

13) Anticoagulation therapy within 7 days of C1D1, including acetylsalicylic acid, low molecular weight heparin, or warfarin

14) Known human immunodeficiency virus (HIV) infection

15) Hepatitis B surface Antigen (HBsAg) positive

16) Hepatitis C virus (HCV) antibody positive with HCV RNA positive

17) Use of moderate/strong cytochrome P450 (CYP) 3A4 inhibitors or moderate/strong CYP3A4 inducers within 2 weeks prior to the first dose of study drug

18) History of high grade esophageal or gastric varices

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

This is an open-label study. All baseline tests and procedures must be completed prior to the administration of the first dose of study drug on Day 1. It is the responsibility of the investigator to ensure that subjects are eligible for the study prior to enrollment. A subject will be considered enrolled once he or she has been randomized.

5.2. Description and Handling of GS-5829

5.2.1. Formulation

GS-5829 will be supplied as GS-5829-02 (phosphate salt form of GS-5829) and is available as round, plain-faced tablets containing 1 mg or 5 mg. The 1 mg tablet is film-coated gray and the 5 mg tablet is film-coated orange.

In addition to the active ingredient, 1 mg tablets contain the following commonly used excipients: microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide black.

In addition to the active ingredient, 5 mg GS-5829 tablets contain the following commonly used excipients: microcrystalline cellulose, lactose monohydrate, crospovidone, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C yellow #6, and iron oxide yellow.

5.2.2. Packaging and Labeling

GS-5829 tablets are provided in white, high density polyethylene bottles with desiccant and polyester packing material. Each bottle contains 30 tablets and is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

Study drug(s) to be distributed to centers in the US and other participating countries shall be labeled to meet applicable requirements of the United States Food and Drug Administration (FDA), EU Guideline to Good Manufacturing Practice – Annex 13 (Investigational Medicinal Products), and/or other local regulations.

5.2.3. Storage and Handling

GS-5829 tablets should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label.

Until dispensed to the subjects, all bottles of study drug should be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability and proper identification, the drug product should not be stored in a container other than the container in

which it was supplied. Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure when handling GS-5829 tablets.

Commercially available product of exemestane and fulvestrant will be used for the study. Further information regarding formulation are available in the Prescribing Information for commercial products.

5.3. Dosage and Administration of GS-5829, Exemestane and Fulvestrant

GS-5829 tablets will be provided by Gilead Sciences, Inc. and will be taken orally. Initiation of treatment with the study drug will take place after enrollment and cohort assignment. Subjects will take their dose of study drug at approximately 24-hour intervals. To reduce inter-subject variability on efficacy and safety, subjects will be instructed to take GS-5829 approximately 1 hour before or 2 hours after a meal. Grapefruit juice is prohibited while on study drug.

GS-5829 tablets will be self-administered orally once daily, beginning on C1D1 of the study and thereafter at approximately the same time each day until EOT.

For subjects in Group A, exemestane 25 mg tablets will be self-administered orally once daily (or in accordance with locally approved labeling), beginning on C1D1 of the study and thereafter at approximately the same time each day until the EOT.

For subjects in Group B, fulvestrant will be administered intramuscularly (in accordance with locally approved labeling) by the clinic staff approximately every 28 days (± 3 days) until the EOT.

For all subjects in the Randomized Phase 2 Dose Expansion phase and for subjects in the Phase 1b Dose Escalation for whom C1D1 is the subject's first dose of fulvestrant, a one-time additional dose of fulvestrant will be administered on Cycle 1, Day 15 (± 3 days).

5.3.1. Dose Adjustment of GS-5829

If at any time in the study, a subject experiences a toxicity consistent with a Grade 4 AE that is deemed to be related to GS-5829, GS-5829 treatment will be discontinued permanently, with the exception of Grade 4 neutropenia, thrombocytopenia, or alopecia. If a subject experiences non-hematologic Grade 3 toxicity consistent with a DLT (per Section 3.2), dosing with GS-5829 will be postponed until the toxicity is resolved to Grade 0 or 1 (as defined by the CTCAE, version 4.03) or returns to the subject's baseline value. If the toxicity resolves to Grade 0 or 1 or returns to the subject's baseline value within 28 days from the start of the event, the subject may resume dosing of GS-5829 at a dose that is at least one dose level lower after discussion with the Gilead medical monitor (See Table 5-1).

If the subject experiences a recurrence of the toxicity after restarting study drug at a lower dose or if the toxicity does not resolve within 28 days, treatment with GS-5829 will be permanently discontinued.

If a subject has Grade 4 neutropenia, Grade 3 neutropenia with fever, or Grade 3 thrombocytopenia, GS-5829 should be interrupted for up to 28 days and/or until the toxicity resolves to ≤ Grade 1. If the Grade 4 neutropenia or Grade 3 fever and neutropenia resolves within 4 days (7 days for Grade 3 thrombocytopenia), then the subject may resume dosing at the same dose. If the Grade 4 neutropenia or Grade 3 fever and neutropenia takes > 4 days (> 7 days for Grade 3 thrombocytopenia), but within 28 days to recover, then the dose of GS-5829 must be resumed at a lower dose. If the Grade 4 neutropenia, Grade 3 fever and neutropenia or Grade 3 or higher thromboctyopenia takes longer than 28 days to recover then GS-5829 must be permanently discontinued. Grade 4 thrombocytopenia observed at any time must be followed by a dose reduction.

If the recurrent toxicity is hematologic a second dose decrease is allowed (lowest dose allowed 1.0 mg) in either total daily dose or by a change in schedule such that the total amount of GS-5829 administered over a 28 day period is decreased by at least 25%.

Table 5-1. Dose Reduction of GS-5829

HEMATOLOGICAL ADVERSE EVENTS	
Neutropenia	
Grade ≤ 3 Neutropenia	Maintain current dose level and schedule.
Grade 4 neutropenia (or occurrence of Grade ≥ 3 neutropenia (ANC < 1000/mm^3) with fever (a single temperature of > 38.3°C or a sustained temperature of ≥ 38°C for more than one hour) or infection	Hold dosing with GS-5829 until the toxicity is resolved to ≤ Grade 1. If the toxicity resolves to ≤ Grade 1 within 4 days, the subject may resume dosing of GS-5829 at the same dose. If recovery to Grade ≤ 1 takes > 4 days, but within 28 days, then the subject may resume dosing of GS-5829 at a dose that is at least one dose level lower after discussion with the Gilead medical monitor. Granulocyte colony-stimulating factor (GCSF) is allowed (but not concurrent with GS-5829)
Thrombocytopenia	
Grade ≤ 2 Thrombocytopenia	Maintain current dose level and schedule.
Grade 3 Thrombocytopenia	Hold dosing with GS-5829 until the toxicity is resolved to ≤ Grade 1. If the toxicity resolves within 7 days, the subject may either resume at the same dose or a dose with is one level lower or at an intermittent dosing schedule (at least 25% less GS-5829 in a 28 day dosing period) after discussion with the Gilead medical monitor. If the thrombocytopenia takes 7-28 days to recover then the subject must resume at a dose one level lower or at an intermittent dosing schedule after discussion with the Gilead medical monitor.
Grade 4 Thrombocytopenia	Hold dosing with GS-5829 until the toxicity is resolved to ≤ Grade 1. If the toxicity resolves within 28 days, the subject may either resume at a dose with is at least one level lower, or at intermittent dosing schedule (at least 25% less GS-5829 in a 28 day dosing period) after discussion with the Gilead medical monitor.

NON-HEMATOLOGICAL ADVERSE EVENTS	
Hepatic Adverse Events (elevations in ALT or AST and/or bilirubin)	
Grade 1 (ALT/AST ≤ 3 x ULN) (Bilirubin ≤ 1.5 x ULN)	Maintain current dose level and schedule.
Grade 2 (ALT/AST > 3-5 x ULN) (Bilirubin>1.5 -≤ 3 x ULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least once a week.
Grade 3	Hold dosing until ≤ Grade 2. Permanently discontinue if any Grade 3 or Grade 4 elevation in AST or ALT associated with a Grade 2 elevation in bilirubin
Grade 4	Permanently discontinue GS-5829
Non-Hepatic, Non-Hematologic Adverse Events	
Grade ≤ 2	No change in dosing required. Dosing may be interrupted until Grade ≤ 1 or baseline
Grade 3	Hold dosing until ≤ Grade 1 and decrease dose by at least one dose level lower or at intermittent dosing schedule (at least 25% less GS-5829 in a 28 day dosing period) after discussion with the Gilead medical monitor.
Grade 4	Permanently discontinue GS-5829

If the toxicity does not resolve or return to baseline, study drug(s) GS-5829 and exemestane or GS-5829 and fulvestrant will be permanently discontinued and the subject will return for an EOT and a 30-day Safety Follow-Up visit.

If the subject was not receiving GS-5829 at the time disease progression was documented (eg, due to reversible toxicity), after discussion with the Gilead medical monitor, GS-5829 may be re-started if the criteria for resuming treatment are met and the investigator feels it is in the subject's best interest to do so.

If a subject develops a recurrence of the same Grade 3 or 4 hematologic or any non-hematologic toxicity that the investigator considers related to GS-5829 and is clinically significant at the lower dose, then the subject should be permanently discontinued from all study drug(s).

After the 28 day DLT period in the Dose Escalation Phase and at any time in the Dose Expansion Phase, in the event of a Grade 2 hematologic or non-hematologic toxicity the investigator considers related to GS-5829, GS-5829 may be interrupted per the investigator's discretion for a maximum of 28 days and resumed at either the same or a lower dose per Table 3-1.

Subjects with a dose interruption for a non-drug related toxicity for up to 28 days, and are deemed by the investigator to be clinically benefiting from GS-5829 prior to dose interruption, may resume GS-5829 treatment. Non-drug related dose interruptions for longer than 28 days in subjects who do not have disease progression may be considered for resumption of GS-5829 after discussion with the Gilead medical monitor.

No dose reduction of GS-5829 below 2 mg is allowed.

Table 5-2. Dose Reduction of GS-5829

Dose at time of toxicity (mg)	Restarting dose level (mg)
9	6
6	4
4	3
3*	2

* Dose level 1

5.3.2. Dose Adjustment of Fulvestrant

Since there is no anticipated drug-drug interaction between GS-5829 and fulvestrant, the dose, route and schedule for administration of fulvestrant in Group A is provided in package insert included in Appendix 9. Dose adjustment for GS-5829 is provided in Section 5.3.1

5.3.3. Dose Adjustment of Exemestane

Since there is no anticipated drug-drug interaction between GS-5829 and exemestane, the dose, route and schedule for administration of exemestane in Group B is provided in package insert included in Appendix 8. Dose adjustment for GS-5829 is provided in Section 5.3.1.

5.4. Prior and Concomitant Medications

Pre-/peri-menopausal subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug. If subjects have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the study on or before C1D1.

Subjects enrolling in the Phase 1b Dose Escalation phase of the study may have progressed on fulvestrant or exemestane as a single agent.

Subjects enrolling in the Randomized Phase 2 Dose Expansion phase of the study may not have received prior exemestane (Group 1) or fulvestrant (Group 2).

In vitro data indicates GS-5829 is a substrate of CYP3A4. Co-administration of CYP3A4 inhibitors may increase GS-5829 exposure. As such, co-administration of moderate and strong CYP3A4 inhibitors with study drug is prohibited in this study.

Co-administration of CYP3A4 inducers may decrease GS-5829 exposure. As such, moderate and potent CYP3A4 inducers are prohibited while subject is on study drug and within 2 weeks prior to study drug. Examples of moderate and strong CYP3A4 inhibitors and inducers are provided in the table below.

Table 5-3. Examples of Concomitant Medications Prohibited in this Study

	Moderate	Strong
CYP3A4 Inhibitor	aprepitant, ciprofloxacin, crizotinib, diltiazem, erythromycin, fluconazole, imatinib, verapamil	clarithromycin, conivaptan, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, voriconazole
CYP3A4 Inducer	bosentan, modafinil, nafcillin	carbamazepine, phenytoin, rifampin, St. John's wort

Toxicology data from dogs demonstrated minimal to moderate gastrointestinal, pulmonary, muscular and intracardiac bleeding. The mechanism for the bleeding is not understood. Anticoagulant medications are prohibited on study. This includes vitamin K antagonists (eg, warfarin), low molecular weight heparin, Factor Xa inhibitors, thrombin inhibitors and aspirin. If anticoagulation therapy needs to be initiated while on study treatment, the investigator should consult with the Gilead medical monitor to determine if study treatment should be discontinued.

5.5. Accountability for GS-5829, Exemestane and Fulvestrant

The investigator is responsible for ensuring adequate accountability of all used and unused investigational medicinal products (IMP). This includes acknowledgement of receipt of each shipment of IMP (quantity and condition). All used and unused IMP dispensed to subjects must be returned to the site.

Study drug (GS-5829, exemestane and fulvestrant) accountability records will be provided to each study site to:

- Record the date received and quantity of study drug kits
- Record the date, subject number, subject initials, the study drug kit number dispensed
- Record the date, quantity of used and unused study drug returned, along with the initials of the person recording the information.

5.5.1. GS-5829, Exemestane and Fulvestrant Investigational Medicinal Product Return or Disposal

Study drugs should be retrieved from each subject at the end of each dispensing interval. The quantity of study drug and the date returned by the subject should be recorded in the study drug accountability records. Whenever possible, study drug returned by the subject should be retained for review by the study site monitor prior to destruction.

For additional information about study drug accountability, return and disposal, refer to Section 9.1.7.

6. STUDY PROCEDURES

The study procedures to be conducted for each subject enrolled in the study are presented in tabular form in Appendix 2 and described in the text that follows. Additional information is provided in the study procedures manual.

The investigator must document any deviation from protocol procedures and notify the sponsor or contract research organization (CRO).

Safety and tolerability assessments will include regular monitoring of AEs, changes from baseline in laboratory variables, physical examinations, vital signs, and special safety assessments like ECGs.

From the time of obtaining informed consent through the first administration of investigational medicinal product, record all serious adverse events (SAEs), as well as any non-serious AEs related to protocol-mandated procedures on the AEs electronic case report form (eCRF). All other untoward medical occurrences observed during the Screening period, including exacerbation or changes in medical history are to be captured on the medical history eCRF. See Section 7 for additional details.

6.1. Subject Enrollment and Treatment Assignment

Subjects will be assigned a unique screening number at the time of consent. Subject eligibility will be established at the conclusion of the screening evaluations. Once eligibility is confirmed, subjects will be assigned a unique subject number. The screening number and/or subject ID will be assigned for that individual subject by Gilead. The investigator will submit an enrollment form to Gilead and/or designee for review and approval prior to enrollment of the subject.

It is the responsibility of the investigator to ensure that each subject is eligible for the study before start of treatment.

6.2. Study Procedures Descriptions

6.2.1. Informed Consent

All subjects must sign and date the most recent Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (IRB/IEC)-approved informed consent form before any study procedures are performed. PPD

Subjects who screen fail must re-sign the informed consent, in the event any screening procedures will be performed outside of the 28-day screening window from the time of the first informed consent.

6.2.2. Medical History

A complete medical history will be obtained by the investigator or qualified designee at screening and recorded on the eCRF. Medical history will include information on the subject's significant past medical events (e.g., prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent illnesses.

6.2.3. Prior and Concomitant Medications

All medications taken up to 30 days prior to the screening visit will be recorded on the eCRF. In addition, supportive therapies given during the course of the study (e.g. blood transfusion, growth factor) should be collected and recorded on the eCRF.

At each study visit, the site will capture any and all medications taken by the subject since the last visit or during the visit (as applicable). Concomitant medications include prescription and non-prescription medications, pre-infusion medications (e.g. anti-emetics), and vitamins and minerals.

6.2.4. Physical Examination

The investigator or qualified designee will perform a complete physical examination at designated time points during the study (Refer to Appendix 2). Pre-dose abnormal findings will be reported on the medical history page of the eCRF. Any changes from the pre-dose baseline physical examination that represent a clinically significant deterioration will be documented on the AE page of the eCRF.

Weight (without shoes) should be measured with each physical examination.

Height (without shoes) should be measured at Screening only.

Beginning at C1D1, a modified physical examination will be performed to monitor for any changes, and will also include weight and assessment of disease-related clinical signs and symptoms.

6.2.5. Vital Signs

Vital signs will include blood pressure, respiratory rate, pulse, and temperature. All measurements will be recorded on the appropriate eCRF page with appropriate source documentation. Any abnormal measurements may be repeated and reported as AEs if appropriate. All measures of blood pressure will be performed using standard sphygmomanometry. Measurements of blood pressure should be taken per institutional guidelines.

6.2.6. Electrocardiogram

Triplicate 12-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at the applicable study visits and transferred to a central vendor for storage. ECGs should always be collected prior to PK (or any other blood draw) if they are to be collected at the same nominal time point. Subjects should be resting quietly and free of distraction (e.g. television, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.

The investigator or qualified designee will review all ECGs. The ECG tracings will be maintained in the source documentation of each subject and the appropriate data reported on the eCRF.

6.2.7. Echocardiogram

Echocardiograms will be performed at the time points listed in the Study Procedures Tables (Appendix 2).

Abnormal echocardiogram findings that are considered clinically significant by the investigator should be reported as AEs and recorded in the AE eCRF if the finding meets the definition of an AE.

6.2.8. ECOG Performance Status

ECOG Performance Status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG will be scored using the scale index in Appendix 6.

6.2.9. Adverse Events

Subjects will be assessed for AEs per guidelines in the National Cancer Institute (NCI) CTCAE (version 4.03) at the time points outlined in Appendix 4. Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. The subject will be assessed for AEs approximately 30 days after the last dose of study drug. Please refer to Appendix 4 CTCAE grading criteria.

Please refer to Section 7 for additional information on AE reporting.

6.2.10. Disease Assessments

6.2.10.1. CT or MRI

Subjects will be assessed by CT scan with contrast (or MRI, if unable to tolerate CT contrast) of the chest, abdomen and pelvis to document metastatic disease, identify target lesions and to assess response as per RECIST 1.1. The same assessment methods should be used for the subject throughout all treatment cycles.

In subjects who cannot tolerate iodinated contrast, a CT of the lung without contrast and MRI of the abdomen should be performed. Imaging by CT scan (with contrast) or MRI or applicable scan will be performed at Screening (within 28 days before C1D1 if the scan was performed as part of standard medical practice) and every 8 weeks for the first year and then every 12 weeks during the treatment period regardless of cycle number or dose interruption. During the treatment, scans may be performed at time points other than 12 weeks, as clinically indicated, to assess tumor progression.

Tumor burden will be characterized at baseline and subsequent response assessments will be carried out according to the RECIST v. 1.1 . The same radiographic procedure and specification (e.g., the same contrast agent, slice thickness, etc.) used to define measurable lesions at baseline must be used throughout the study for each subject.

Subjects who discontinue study treatment for reasons other than disease progression will continue to have tumor assessments performed during the follow up visits every 12 weeks until initiation of new anti-cancer therapy, or discontinuation from the overall study participation (death, subject's request, lost to follow-up).

6.2.10.2. Bone Scans

Subjects will undergo radionuclide bone scan at Screening (within 28 days before C1D1 if the scan was performed as part of standard medical practice) and every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of randomization during the treatment period. Scans at the EOT visit are not necessary if the prior scan was performed within 4 weeks prior to the EOT visit date.

Bone lesions imaging:

- If bone lesions were identified at baseline as the only sites of a subject's disease the following assessment must be performed:
    - CT scan/MRI every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of randomization and to confirm CR using the same modality used to confirm the bone lesions at baseline. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
- If no bone lesions were identified at baseline, or if bone is not the only site of a subject's disease, bone scans will only be repeated as clinically indicated (ie, subject describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required to confirm CR. Abnormalities found on subsequent bone scans shall also be confirmed by X-ray, CT or MRI.

6.2.11. Laboratory Assessments

Screening laboratory samples should be obtained within 28 days prior to C1D1 dose (GS-5829). Local laboratory complete blood count (CBC) assessments may be collected as required for dose adjustments throughout the study. Local laboratory assessments resulting in a dose change will be reported on the eCRF.

The central laboratory will be responsible for chemistry, hematology, and coagulation testing per Table 6-1 and storage of other study samples. If central laboratory results are not available, local laboratories may be used for dosing decision. Other tests listed in Table 6-1 will be performed by Gilead or a designated laboratory. Any sample collected per the Schedule of Assessments (Appendix 2) may be analyzed for any tests necessary to ensure subject safety. Specific instructions for processing, labeling, and shipping samples will be provided in the central laboratory manual. The date and time of sample collection will be recorded in the subject's source documentation and reported to the central laboratory.

The date and time of previous GS-5829 dose will be recorded in the subject's source documentation on days where PK is collected. WBC differentials will be reported as absolute counts. All laboratory tests must be reviewed for clinical significance by the investigator or qualified designee. Eligibility will be based on central laboratory assessments and will be collected within 7 days of C1D1.

C1D1 pre-dose samples may be drawn up to 2 days prior to the visit.

The analytes listed in Table 6-1 will be tested.

Table 6-1. Analytes

Serum Chemistry	Hematology	Other
Sodium Potassium Chloride Glucose BUN Creatinine Creatinine Clearance[a] ALT AST Alkaline phosphatase Total bilirubin[b] Total protein Albumin Calcium Magnesium Phosphate AAG CRP	White Blood Cell (WBC) Count Hemoglobin Hematocrit Platelet Count Neutrophils (ANC) Lymphocytes Monocytes Basophils Eosinophils	Serum β-hCG for pregnancy test GS-5829 concentration Concentrations of GS-5829 metabolite(s), fulvestrant, exemestane, and/or metabolites, as applicable, may be determined PPD Hepatitis B surface antigen Hepatitis C antibody FSH Serum Estradiol Hepatitis C RNA Reflex 26- hydroxyvitamin D
	Coagulation	
	PT/INR aPTT	

a Cockcroft-Gault using Actual Body Weight: CRCL (mL/min) = [(140-age(years)) * weight(kg)] / (serum creatinine (mg/dL)*72)
b Includes direct bilirubin

6.2.12. Pregnancy Test for Females of Childbearing Potential

All female subjects of childbearing potential (as defined in Appendix 5) will have serum pregnancy, estradiol and FSH testing throughout the study (refer to Appendix 2). The results must be confirmed as negative for pregnancy prior to continued administration of study drug.

Female subjects of childbearing potential must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug.

6.2.13. Vitamin D Assessment

Routine assessment of 25-hydroxy vitamin D levels prior to the start of exemestane and fulvestrant treatment should be performed, due to the high prevalence of vitamin D deficiency in women with breast cancer. Women with vitamin D deficiency should receive supplementation with vitamin D.

6.2.14. Pharmacokinetic & Pharmacodynamic Samples

PK samples will be collected at the time points listed below for each Phase. GS-5829 plasma concentrations will be determined using a validated assay. Plasma concentrations of GS-5829 metabolites and/or exemestane and/or fulvestrant metabolites may be determined. Plasma protein binding of analytes may be evaluated. PD samples may be modified based on the emerging data.

Phase 1b Dose Escalation

PK and PD samples for GS-5829 will be collected on Day 1 and Day 15 of Cycle 1 at pre-dose 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post-dose and anytime on Day 1 of Cycles 2 through 6. Refer to Appendix 3.

Randomized Phase 2 Dose Expansion

Sparse PK and PD samples will be collected at pre-dose and anytime between 1 to 4 hours post-dose on Day 1 and Day 15 of Cycle 1 and at pre-dose on Day 1 of Cycles 3 and 6. Refer to Appendix 3. Note: PK samples will only be collected for subjects who are randomized to a GS-5829 combination arm.

6.3. Biomarker Testing

6.3.1. Biomarker Samples to Address the Study Objectives:

PPD

PPD

PPD

PPD

PPD

6.4. Re-Screening Criteria

Subjects who do not enroll within 28 days of screening will be screen failed.

Re-screening may be allowed. Subjects who are re-screened will be re-consented with new screening number, and will repeat the screening assessments. Subjects who do not meet QTc criteria are not allowed to re-screen (see Section 4.3). Gilead is to be informed prior to a subject re-screening.

6.5. Treatment Assessments

Each on-study visit will be scheduled relative to C1D1. Visits will follow the schedule of assessments in Appendix 2 and Appendix 3.

Subjects who meet eligibility criteria will receive GS-5829 orally once daily combined with daily orally dosing of either exemestane or injection of fulvestrant intramuscularly on Day 1, Day 28 and then every 28 days (± 3 days). Subjects initiating fulvestrant on C1D1 should receive a single additional dose at C1D15. Subjects in the Phase 1b Dose Escalation phase of the study may initiate exemestane (Group A) or fulvestrant (Group B) any time prior to, or on, C1D1. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including an assessment of tumor response, physical exam, vitals, ECG, collection of blood samples (for routine safety labs, GS-5829 PK, PD markers, and biomarkers at applicable visits), and assessment of AEs. In addition, subjects will undergo a CT scan (or MRI) scan every 8 weeks for the first year and then every 12 weeks. Bone scans may be repeated as clinically indicated or to confirm a CR. A subject who does not show evidence of disease progression may continue receiving GS-5829 once daily and exemestane (Group 1) or fulvestrant (Group 2) until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.

After discontinuation of study treatment, subjects will be followed for safety for 30 days and up to two years for OS.

6.6. Post-treatment Assessments

All subjects will complete the 30-Day Safety Follow-Up Visit. For Phase 1b Dose Escalation subjects, the 30-Day Safety Follow-Up will be the final study visit. Randomized Phase 2 Dose Expansion subjects will complete the 30-Day Safety Follow-Up Visit and proceed to Long Term Survival Follow-Up.

Subjects who discontinue study treatment for reasons other than disease progression will continue to have tumor assessments performed during the follow up visits every 12 weeks until initiation of new anti-cancer therapy, or discontinuation from the overall study participation (death, subject's request, lost to follow-up).

6.7. Long-Term Survival Follow-Up

Randomized Phase 2 Dose Expansion subjects will participate in long-term survival follow-up. These subjects will be contacted via phone call every 3 months for determination of long- term survival status and record of any other anti-cancer therapy for up to 2 years after the last dose of IP. For subjects who discontinued the study for reasons other than disease progression, the investigator should obtain information on the subject's post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

Subjects who are alive at the time the sponsor has made the determination the study will be ended will receive a final follow-up phone call to assess survival status and communicate the sponsor's decision. These subjects will be censored on the date the subject was last contacted.

The investigator will make every effort to contact the subject or a close relative or caretaker by phone to collect survival information. The investigator should show due diligence by documenting in the source documents steps taken to contact the subject i.e., dates of phone calls, registered letters, etc.

6.8. Unscheduled Visits

Unscheduled procedures may occur at any time during the study. Vital Signs, ECOG, ECHO, 12-lead ECG, bone scan and CT or MRI, may be conducted at these visits and recorded on the applicable eCRFs.

6.9. Assessments for Premature Discontinuation from Study

If a subject discontinues study dosing (for example, as a result of an AE), every attempt should be made to keep the subject in the study and continue to perform the required study-related follow-up and procedures (see Section 6.10, Criteria for Discontinuation of Study Treatment). If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study.

6.10. Criteria for Discontinuation of Study Treatment

See Section 3.5 for discontinuation criteria.

6.11. Post Study Care

If a subject has discontinued the study treatment due to toxicity, he/she should not have withdrawal of consent recorded as the reason for discontinuation. Instead, the reason for discontinuation must be recorded as due to AEs.

Every attempt should be made to keep the subject in the study and continue collecting CT or MRI scans for tumor assessment at every 8 weeks for the first year and then every 12 weeks from the date of randomization until disease progression or initiation of systemic anti-tumor therapy other than treatment per protocol. If this is not possible or acceptable to the subject or investigator, the subject may be withdrawn from the study. The subject will be asked to attend

the post-treatment follow-up assessment visit above when discontinuing from the study treatment. Randomized Phase 2 Dose Expansion subjects will participate in long-term survival follow-up. These subjects will be contacted via phone call every 3 months for determination of long- term survival status and record of any other anti-cancer therapy for up to 2 years after the last dose of IP.

6.12. Replacement of Subjects

If a subject in the Phase Ib portion of the study is withdrawn from the study for any reason other than a DLT prior to completion of the DLT assessment window, a replacement subject will be enrolled at the same dose level as the replaced subject. To be evaluable for the DLT observation, a subject must receive at least 21 doses of GS-5829, complete all safety procedures through Day 28, or experience a DLT prior to Day 28.

6.13. Protocol Deviations

Gilead's policy prohibits exemptions from protocol inclusion/exclusion criteria. In the event of a significant deviation related to gross non-compliance from the protocol or incidences that impose significant risk to subject safety, the investigator or designee must notify the sponsor and/or its designee immediately. The site will be required to document deviations in accordance with Gilead's procedures and in accordance with the site's procedures and processes.

6.14. End of Study

End of study for a subject is defined as the date of the last study-related procedure or the date of death for an on-study subject. Randomized Phase 2 Dose Expansion subjects will participate in long-term survival follow-up. These subjects will be contacted via phone call every 3 months for determination of long- term survival status and record of any other anti-cancer therapy for up to 2 years after the last dose of IP.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1. Definitions of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1. Adverse Events

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs may also include pre- or post-treatment complications that occur as a result of protocol specified procedures, lack of efficacy, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.

7.1.2. Serious Adverse Events

A SAE is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization

- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes constituting SAEs. Medical and scientific judgment must be exercised to determine whether such an event is a reportable under expedited reporting rules. Examples of medically important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse. For the avoidance of doubt, infections resulting from contaminated medicinal product will be considered a medically important event and subject to expedited reporting requirements.

7.1.2.1. Protocol-Specific Serious Adverse Event Instructions

To maintain the integrity of the study, disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drugs caused or contributed to the disease progression (ie, by a means other than lack of effect). Unrelated disease progression should be captured on the eCRF.

In addition, events that are indicative of the following disease-related SAEs that are assessed as unrelated to study drugs will not be reported as expedited reports by Gilead during the study:

- Progression of disease
- Death related to disease progression

These events will be exempt from global expedited reporting requirements for the duration of the study as they are the primary endpoints of this study. They will be reported as appropriate in the final clinical study report as well as any relevant aggregate safety report.

7.1.3. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (eg, clinical chemistry, hematology) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (eg, electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (i.e., decreased hemoglobin).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 5.3.1.

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity, and for final review and confirmation of accuracy of event information and assessments.

7.2.1. Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to IMP therapy using clinical judgment and the following considerations:

- **No**: Evidence exists that the AE has an etiology other than the IMP. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the investigational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- **No: Evidence** exists that the AE has an etiology other than the study procedure.

- **Yes:** The AE occurred as a result of protocol procedures, (eg., venipuncture)

7.2.2. Assessment of Severity

The severity of AEs will be graded using the CTCAE, Version 4.03 (Appendix 4).

For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7-1.

Table 7-1. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 7.1.2.

7.3. Investigator Requirements and Instructions for Reporting Adverse Events and Serious Adverse Events to Gilead

Requirements for collection prior to study drug initiation:

After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and AEs related to protocol-mandated procedures.

Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30-days after last administration of study IMP must be reported to the eCRF database as instructed.

All AEs should be followed up until resolution or until the AE is stable, if possible. Gilead Sciences may request that certain AEs be followed beyond the protocol defined follow up period.

Serious Adverse Events

All SAEs, regardless of cause or relationship, that occurs after the subject first consents to participate in the study (ie, signing the informed consent) and throughout the duration of the study, including the protocol-required post treatment follow-up period, must be reported to the CRF/eCRF database and Gilead Drug Safety and Public Health (DSPH) as instructed. This also includes any SAEs resulting from protocol-associated procedures performed after informed consent is signed.

Any SAEs and deaths that occur after the post treatment follow-up visit but within 30 days of the last dose of study IMP, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period, however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of IMP, he/she should promptly document and report the event to Gilead DSPH.

- All AEs and SAEs will be recorded in the eCRF database within the timelines outlined in the eCRF completion guideline.

Electronic Serious Adverse Event (eSAE) Reporting Process

- Site personnel record all SAE data in the eCRF database and from there transmit the SAE information to Gilead DSPH within 24 hours of the investigator's knowledge of the event. Detailed instructions can be found in the eCRF completion guidelines.

- If for any reason it is not possible to record the SAE information electronically, ie, the eCRF database is not functioning, record the SAE on the paper SAE reporting form and submit within 24 hours to:

  Gilead DSPH: Fax: PPD
  Email: PPD

- As soon as it is possible to do so, any SAE reported via paper must be transcribed into the eCRF Database according to instructions in the eCRF completion guidelines.

- If an SAE has been reported via a paper form because the eCRF database has been locked, no further action is necessary.

- For fatal or life-threatening events, copies of hospital case reports, autopsy reports, and other documents are also to be submitted by e-mail or fax when requested and applicable. Transmission of such documents should occur without personal subject identification, maintaining the traceability of a document to the subject identifiers.

- Additional information may be requested to ensure the timely completion of accurate safety reports.

- Any medications necessary for treatment of the SAE must be recorded onto the concomitant medication section of the subject's CRF/eCRF and the event description section of the SAE form.

7.4. Gilead Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, Gilead may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), Gilead or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by Gilead using reference safety information specified in the investigator's brochure or relevant local label as applicable.

All investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

7.5. Toxicity Management

Treatment-emergent toxicities will be noted by the investigator and brought to the attention of the Gilead medical monitor or designee. Whether or not considered treatment-related, all subjects experiencing AEs must be monitored periodically until symptoms subside, any abnormal laboratory values have resolved or returned to baseline levels or they are considered irreversible, or until there is a satisfactory explanation for the changes observed.

Grade 3 or 4 clinically significant laboratory abnormalities should be confirmed by repeat testing as soon as practical to do so, and preferably within 3 calendar days after receipt of the original test results. Any questions regarding toxicity management should be directed to the Gilead medical monitor or designee.

7.6. Special Situations Reports

7.6.1. Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of AEs associated with product complaints, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject, or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose as per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

7.6.2. Instructions for Reporting Special Situations

7.6.2.1. Instructions for Reporting Pregnancies

The investigator should report pregnancies in female study subjects that are identified after initiation of study medication and throughout the study, including the post study drug follow-up period, to Gilead DSPH using the pregnancy report form within 24 hours of becoming aware of the pregnancy.

Refer to eCRF completion guidelines for full instructions on the mechanism of pregnancy reporting.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 7.1.2 Furthermore, any SAE occurring as an adverse pregnancy outcome post study must be reported to Gilead DSPH.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy. The outcome should be reported to Gilead DSPH using the pregnancy outcome report form. If the end of the pregnancy occurs after the study has been completed, the outcome should

be reported directly to Gilead DSPH. Gilead DSPH contact information is as follows: Email: PPD and Fax: PPD

Refer to Appendix 5 for Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements.

7.6.2.2. Reporting Other Special Situations

All other special situation reports must be reported on the special situations report form and forwarded to Gilead DSPH within 24 hours of the investigator becoming aware of the situation. These reports must consist of situations that involve study IMP and/or Gilead concomitant medications, but do not apply to non-Gilead concomitant medications.

Special situations involving non-Gilead concomitant medications does not need to be reported on the special situations report form; however, for special situations that result in AEs due to a non-Gilead concomitant medication, the AE should be reported on the AE form.

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to eCRF completion guidelines for full instructions on the mechanism of special situations reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1. Analysis Objectives and Endpoints

8.1.1. Analysis Objectives

The primary objective:

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

- To determine the MTD or RP2D of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa, as measured by PFS

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by PFS

Secondary objectives:

Phase 1b Dose Escalation

- To evaluate the PK of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced ER+/HER2- BrCa

Randomized Phase 2 Dose Expansion

- To evaluate the efficacy of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa, as measured by ORR and CBR evaluated according to RECIST v. 1.1. ORR is defined as the proportion of subjects with response (CR, or PR). CBR is defined as proportion of subjects with CR, PR, or SD that lasts for ≥ 24 weeks.ER+/HER2- BrCa

- To evaluate the efficacy of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa, as measured by ORR and CBR

- To evaluate the safety and tolerability of GS-5829 in combination with exemestane compared to exemestane alone in subjects with advanced ER+/HER2- BrCa

- To evaluate the safety and tolerability of GS-5829 in combination with fulvestrant compared to fulvestrant alone in subjects with advanced ER+/HER2- BrCa

- To evaluate the OS for subject with advanced ER+ BrCa with exemestane or fulvestrant ± GS 5829

Exploratory objectives:

8.1.2. Primary Endpoint

Phase 1b Dose Escalation:

- Safety profile and tolerability of the combination of GS-5829 and exemestane or fulvestrant as assessed by the incidence of dose limiting toxicities (DLTs) through Day 28 at each dose level of GS-5829

Randomized Phase 2 Dose Expansion:

- PFS defined as the interval from the first dose date to the earlier of the first documented confirmed disease progression or death from any cause

8.1.3. Secondary Endpoint

Phase 1b Dose Escalation:

- GS-5829 PK parameters (e.g. C_{max}, AUC_{tau})

Randomized Phase 2 Dose Expansion:

- Overall safety profile will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study treatment of any AEs or abnormalities in laboratory tests or ECGs

- ORR, defined as the proportion of subjects who achieve CR, PR and SD, based on RECIST v. 1.1 study progression criteria

- CBR, defined as the proportion of subjects who achieve CR, PR or SD that lasts for >24 weeks based on RECIST v. 1.1 study progression criteria

- Overall survival, defined as interval from first dose date to date of death from any cause

8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Intent-to-Treat (ITT) Analysis Set

The ITT analysis set includes all subjects who are randomized in the Randomized Phase 2 Dose Expansion phase of the study regardless of whether subjects receive any study drug(s), or receive a different regimen from the regimen they were randomized to. Treatment assignment will be designated according to randomization.

This analysis set will be used in the analyses of PFS, ORR, and CBR. Subjects in the ITT analysis set who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status will be included in the denominators in the calculation of ORR and CBR.

8.2.1.2. The Per-Protocol (PP) analysis set

The PP analysis set includes data from subjects in the ITT analysis set who meet the general criteria defining the target population for this study: those who are adherent to the protocol, are compliant with study drug treatment, and are evaluable for relevant efficacy endpoints. Treatment assignment will be designated according to the actual treatment received. The PP analysis set will be used in sensitivity analyses of efficacy endpoints.

8.2.1.3. Safety Analysis Set

The Safety Analysis Set includes subjects who receive ≥ 1 dose of study drug. This analysis set will be used for the analyses of safety endpoints, study treatment administration and study drug compliance.

8.2.1.4. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all Phase 1b Dose Escalation subjects in the Safety Analysis Set who complete all treatment and safety procedures through Day 28, or experienced a DLT prior to Day 28. Subjects who are not evaluable for DLT determination may be replaced.

8.2.1.5. Pharmacokinetics and Pharmacodynamics Analysis Sets

The PK and PD Analysis Sets will consist of all subjects in the Safety Analysis Set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.2.1.6. Biomarker Analysis Set

The Biomarker Analysis Sets include data from subjects in the Safety analysis set who have the necessary baseline and on-study measurements to provide interpretable results for the specific parameters of interest.

8.3. Data Handling Conventions

Subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation (StD), 90% confidence intervals (CIs) on the mean, median, the first and third quartiles, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 90% CIs on the percentage. Unless otherwise indicated, 90% CIs for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by relevant dose level (Phase 1b Dose Escalation), time point and treatment groups for the corresponding analysis sets. As appropriate, changes from baseline to each subsequent time point will be described and summarized by dose level. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by dose level. Graphical techniques (eg, waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

8.4. Demographic Data and Baseline Characteristics

Subject demographic and baseline characteristics will be listed and summarized by dose level (Phase 1b Dose Escalation) and by treatment group for the Safety Analysis Set.

8.5. Efficacy Analysis

8.5.1. Primary Analysis

The difference in PFS between the treatment arms will be assessed in the ITT analysis set using Kaplan-Meier methods and the log-rank test. Kaplan-Meier estimates and plots, hazard ratios and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

Subjects who withdraw from the study or are lost to follow-up without disease progression or death will be censored on the date of the last visit when lack of disease progression was documented. Subjects who have progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of

definitive progression was objectively documented. Subjects without any adequate post-baseline disease assessment will be censored on the date of first study dose.

In the sensitivity analysis, PFS will be compared between the treatment arms in the Per-Protocol (PP) analysis set using Kaplan-Meier methods and the log-rank test.

8.5.2. Secondary Analyses

The best overall response will be summarized by each response category as CR, PR, SD and PD by treatment arms. Fisher's exact test will be used to compare ORR and CBR between treatment arms. The 2-sided 95% CIs for ORR and CBR will be calculated based on exact method.

The difference in OS between the treatment arms will be assessed using the log-rank test. Kaplan-Meier estimates and plots, hazard ratios and corresponding 95% CIs (as calculated using a Cox proportional hazards regression model) will be presented.

8.6. Safety Analysis

Safety will be evaluated by assessment of clinical laboratory tests, physical examination, 12-lead ECG, vital signs measurements and documented AEs as described in the Study Procedures Table (Appendix 2). All safety data collected on or after the date that study drug was first dispensed up to the date of last dose of study drug plus 30 days will be summarized by dose level (Phase 1b Dose Escalation) and visit where appropriate and by treatment group for subjects in the Safety Analysis Set. AEs occurred in pretreatment will be included in data listings.

8.6.1. Extent of Exposure

A subject's extent of exposure to GS-5829, exemestane and fulvestrant will be reported. Exposure data and study drug compliance will be summarized by treatment group for subjects in the safety analysis set.

GS-5829 compliance will be described in terms of the amount actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed reductions and interruptions).

Exemestane and fulvestrant compliance will be described in terms of the number of doses actually administered relative to the expected number of doses planned, and as the cumulative dose actually administered relative to the planned cumulative dose.

8.6.2. Adverse Events

The focus of AE summarization will be on treatment-emergent AEs. Treatment-emergent AEs (TEAEs) are events in a given study period that meet one of the following criteria:

- Events with onset dates on or after the start of treatment and up to 30 days after the permanent discontinuation of the study treatment.

- AEs resulting in treatment discontinuation after the start of treatment.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (http://www.meddramsso.com) with descriptions by System Organ Class (SOC), High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of AEs will be graded by the investigator according to the CTCAE, Version 4.03, whenever possible. If a CTCAE criterion does not exist for a specific type of AE, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the AE: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the AE to the IP will be categorized as related or unrelated. TEAEs will be summarized by dose level (Phase 1b Dose Escalation). Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages.

Following summaries (number and percentage of subjects) of TEAEs will be provided:

1. All AEs
2. AEs related to study drug
3. AEs that are Grade ≥ 3 in severity
4. AEs leading to study drug modification (interruption/reduction)
5. AEs leading to study drug discontinuation
6. AEs leading to death
7. SAEs

Summaries of TEAEs (by SOC and PT) will be provided by dose level (Phase 1b Dose Escalation) and treatment group. A subject who reports multiple treatment-emergent AEs within the same Preferred Term (or SOC) is counted only once for that Preferred Term (or SOC) using the worst severity grade.

All AEs will be listed.

8.6.3. Laboratory Evaluations

All central laboratory results will be listed. Selected laboratory data will be summarized using only observed data. Laboratory results and change from baseline at all scheduled time points will be summarized.

The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsened by ≥ 1 grade in the period from the first dose of study treatment to 30 days after the last dose of study drug. If baseline measurement is missing, then any graded

abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Hematology and serum biochemistry will be graded according to CTCAE 4.03 severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the central laboratory will be used to determine whether a laboratory value is below, within, or above the normal range for the subject's age, sex, etc.

Hematology and serum biochemistry test results and their changes from baseline will be summarized by dose level Phase 1b Dose Escalation, visit and treatment group. Laboratory abnormalities will be summarized for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (e.g., during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.6.4. Other Safety Evaluations

Dose limiting toxicities will be listed for all dose levels.

8.7. Pharmacokinetic Analysis

In the Phase 1b Dose Escalation portion of study, the plasma concentration of GS-5829 will be summarized by nominal sampling time using descriptive statistics by dose cohorts. Pharmacokinetic parameters will be determined using standard non-compartmental methods. PK parameters (C_{max} and, AUC_{tau}), will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%) StD, median, minimum, and maximum) by dose cohorts. Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± StD, and median (Q1, Q3) if applicable. In the Randomized Phase 2 Dose Expansion portion of study, plasma concentrations will be summarized by nominal sampling time using descriptive statistics by treatment arm.

8.8. Biomarker Analysis

Descriptive statistics of baseline and change in biomarkers will be provided at each sampling time for all subjects, and by treatment arms.

PPD

PPD

8.9. Sample Size

The sample size of the Phase 1b Dose Escalation portion of the study will be determined based on the number of dose levels evaluated and the emerging drug-related toxicities, and may enroll up to approximately 60 subjects.

Approximately 120 subjects will be enrolled in the Randomized Phase 2 Dose Expansion portion of this study. Approximately 60 subjects will be randomized to receive GS-5829 in combination with exemestane or exemestane alone in a 2:1 ratio. Similarly, in Group 2 of the Randomized Phase 2 Dose Expansion portion of the study, approximately 60 subjects will be randomized to receive GS-5829 in combination with fulvestrant or fulvestrant alone in a 2:1 ratio. The sample size of 60 subjects (40 in the combination arm and 20 in the exemestane alone or fulvestrant alone arm) will provide 37 events in total and greater than 80% power to detect the difference in PFS between GS-5829 in combination with exemestane and exemestane alone and between GS-5829 in combination with fulvestrant and fulvestrant alone with 0.1 two-sided significance level, assuming a median PFS of 5 months for subjects who receive exemestane alone or fulvestrant alone, a median PFS of 12.5 months in subjects who receive GS-5829 in combination with exemestane or fulvestrant, accrual period of 6 months, total study duration of 18 months and a drop-out rate of 10% by 12 months.

An interim analysis may be performed separately when 22 events have been reached in each group. The purpose of this analysis is to have an early evaluation of the safety and efficacy of GS-5829 in combination with exemestane or fulvestrant. The interim analysis will assess either an expansion or study stop on any one of the arms independent of one another. The trial will continue after the interim analysis.

9. RESPONSIBILITIES

9.1. Investigator Responsibilities

9.1.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. These standards are consistent with the European Union Clinical Trials Directive 2001/20/EC and GCP Directive 2005/28/EC.

The investigator will ensure adherence to the basic principles of GCP, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998.

The investigator and all applicable sub-investigators will comply with 21 CFR, Part 54, 1998, providing documentation of their financial interest or arrangements with Gilead, or proprietary interests in the investigational drug under study. This documentation must be provided prior to the investigator's (and any sub-investigator's) participation in the study. The investigator and sub-investigator agree to notify Gilead of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date when the last subject completes the protocol-defined activities.

9.1.2. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Review and Approval

The investigator (or sponsor as appropriate according to local regulations) will submit this protocol, informed consent form, and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) to an IRB/IEC. The investigator will not begin any study subject activities until approval from the IRB/IEC has been documented and provided as a letter to the investigator.

Before implementation, the investigator will submit to and receive documented approval from the IRB/IEC any modifications made to the protocol or any accompanying material to be provided to the subject after initial IRB/IEC approval, with the exception of those necessary to reduce immediate risk to study subjects.

9.1.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB or IEC approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by local requirements. The consent form will inform subjects about genomic testing and sample retention, and their right to receive clinically relevant genomic analysis results.

9.1.4. Confidentiality

The investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject initials, date of birth, another unique identifier (as allowed by local law) and an identification code will be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. Laboratory specimens must be labeled in such a way as to protect subject identity while allowing the results to be recorded to the proper subject. Refer to specific laboratory instructions. NOTE: The investigator must keep a screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial. Subject data will be processed in accordance with all applicable regulations

The investigator agrees that all information received from Gilead, including but not limited to the investigator brochure, this protocol, eCRF, the IMP, and any other study information, remain the sole and exclusive property of Gilead during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Gilead. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

9.1.5. Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: (1) investigator's study file, and (2) subject clinical source documents.

The investigator's study file will contain the protocol/amendments, CRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include sequential notes containing at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, ie, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Documentation of the reason(s) a consented subject is not enrolled
- Participation in study (including study number);
- Study discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end date (including dose regimen) of IMP, including dates of dispensing and return;
- Record of all AEs and other safety parameters (start and end date, and including causality and severity);
- Concomitant medication (including start and end date, dose if relevant; dose changes);
- Date of study completion and reason for early discontinuation, if it occurs.

All clinical study documents must be retained by the investigator until at least 2 years or according to local laws, whichever is longer, after the last approval of a marketing application in an ICH region (ie, United States, Europe, or Japan) and until there are no pending or planned marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if specified by regulatory requirements, by local regulations, or by an agreement with Gilead. The investigator must notify Gilead before destroying any clinical study records.

Should the investigator wish to assign the study records to another party or move them to another location, Gilead must be notified in advance.

If the investigator cannot provide for this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Gilead to store these records securely away from the site so that they can be returned sealed to the investigator in case of an inspection. When source documents are required for the continued care of the subject, appropriate copies should be made for storage away from the site.

9.1.6. Case Report Forms

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRF should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data. The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor or internal Gilead staff, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Gilead will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements outlined in Section 9.1.5.

9.1.7. Investigational Medicinal Product Accountability and Return

Where possible, study drug(s) should be destroyed at the site. At the start of the study, the study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for disposal or return of unused study drug supplies. If the site has an appropriate standard operating procedure (SOP) for drug destruction as determined by Gilead Sciences, the site may destroy used (empty or partially empty) and unused study drug supplies as long as performed in accordance with the site's SOP. This can occur only after the study monitor has performed drug accountability during an on-site monitoring visit.

A copy of the site's study drug Disposal SOP or written procedure (signed and dated by the PI or designee) will be obtained for Gilead site files. If the site does not have acceptable procedures in place, arrangements will be made between the site and Gilead Sciences (or Gilead Sciences' representative) for return of unused study drug supplies.

If study drug is destroyed on site, the investigator must maintain accurate records for all study drugs destroyed. Upon study completion, copies of the study drug accountability records must be filed at the site. Another copy will be returned to Gilead.

The study monitor will review study drug supplies and associated records at periodic intervals.

9.1.8. Inspections

The investigator will make available all source documents and other records for this trial to Gilead's appointed study monitors, to IRBs, IECs, or to regulatory authority or health authority inspectors.

9.1.9. Protocol Compliance

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.2. Sponsor Responsibilities

9.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by Gilead. The investigator must submit all protocol modifications to the IRB or IEC in accordance with local requirements and receive documented IRB or IEC approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report (CSR) will be prepared and provided to the regulatory agency(ies). Gilead will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of Gilead in an abstract, manuscript, or presentation form or the study has been completed at all study sites for at least 2 years.

- The investigator will submit to Gilead any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation.

- No such communication, presentation, or publication will include Gilead's confidential information.

- The investigator will comply with Gilead's request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

9.3. Joint Investigator/Sponsor Responsibilities

9.3.1. Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol, e.g. attendance at Investigator's Meetings. If required under the applicable statutory and regulatory requirements, Gilead will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.2. Access to Information for Monitoring

In accordance with regulations and guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the accuracy of the data recorded in the eCRF.

The monitor is responsible for routine review of the eCRF at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRF. The investigator agrees to cooperate with the monitor to ensure that any problems detected through any type of monitoring (central, on site) are resolved.

9.3.3. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of Gilead may conduct inspections or audits of the clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the Gilead medical monitor immediately. The investigator agrees to provide to representatives of a regulatory agency or Gilead access to records, facilities, and personnel for the effective conduct of any inspection or audit.

9.3.4. Study Discontinuation

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, Gilead and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. REFERENCES

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
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FOSTER CITY, CA 94403

STUDY ACKNOWLEDGEMENT

A Phase 1b Study Followed by an Open label, Parallel, Randomized Phase 2 Study Evaluating the Safety, Tolerability and Efficacy of GS-5829 in Combination with Exemestane or Fulvestrant Comparing with Exemestane or Fulvestrant Alone in Subjects with Advanced Estrogen Receptor Positive HER2-Negative Breast Cancer

GS-US-350-1937, Original Protocol, 17 June 2016

This protocol has been approved by Gilead Sciences, Inc. The following signature documents this approval.

PPD

PPD
Gilead Sciences, Inc.

PPD

June 17, 2016
Date

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Gilead Sciences, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

Principal Investigator Name (Printed) Signature

Date Site Number

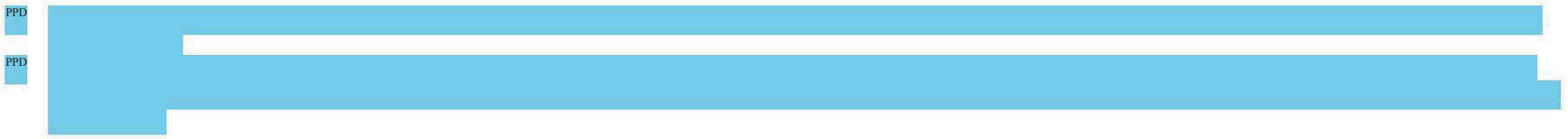
Appendix 2. Study Procedures Table

Study Phase	Screening	Treatment Period					End of Treatment	30 Day Safety Follow Up[9]	Long Term Follow Up[10]
Cycle Day	Day -28	Cycle 1		Cycle 2		Cycle 3 and every 4 weeks			
		Day 1[8]	Day 15	Day 1	Day 15	Day 1			
Window (days)	-28	+3	±2	+3	±2	+3	±7		
Informed Consent [1]	X								
Medical and Medication History [2]	X								
Physical Examination [3]	X	X		X		X	X	X	
ECOG Performance Status [4]	X	X		X			X	X	
Vital Signs [5]	X	X	X	X	X	X	X	X	
Triplicate 12-lead ECG [6]	X	X	X	X		X	X		
Echocardiogram [7]	X			X			X		
Adverse Events/Concomitant Medication [11]	X	X	X	X	X	X	X	X	
GS-5829 Accountability Dispensing [12]		X		X		X	X		
Exemestane or Fulvestrant Administration [13]		Subjects will self-administer exemestane orally once daily starting on or before C1D1. Subjects will receive fulvestrant on C1D1 and every 28 days (+/- 3 days). For subjects initiating fulvestrant on this study, a single dose of fulvestrant should be administered on C1D15 (+/- 3 days).							
Dosing Diary Accountability [14]		X				X	X		
CBC with Differential [15]	X	X	X	X		X	X	X	

Study Phase	Screening	Treatment Period					End of Treatment	30 Day Safety Follow Up[9]	Long Term Follow Up[10]
Cycle Day	Day -28	Cycle 1		Cycle 2		Cycle 3 and every 4 weeks			
		Day 1[8]	Day 15	Day 1	Day 15	Day 1			
Chemistry [15]	X	X	X	X	X	X	X	X	
Coagulation[16]	X	X	X	X			X		
25-hydroxy vitamin D	X								
Serum Pregnancy Test, Serum Estradiol and FSH (if applicable) [17]	X						X		
HBV, HCV, HIV Virology [18]	X								
Archival Tumor Tissue [19]	X								
PPD									
Treatment Response Assessment[20]		Performed every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of randomization					X		
CT/MRI [21]	X						X		
Radionuclide Bone Scan [22]	X						X		
Phone Call									X
PPD									
PPD									

1 Subjects who screen fail must re-sign the informed consent, in the event any screening procedures will be performed outside of the 28-day screening window from the time of the first informed consent.
2 Medical history includes significant past medical events (e.g., prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, historical PSA levels and any concurrent medical illnesses. At screening, all medications taken up to 30 days prior to screening will be documented in the eCRF.
3 Screening and EOT Physical Examinations (PE) will be a complete PE. Beginning at C1D1, a modified physical examination will be performed. Weight (without shoes) should be measured at each PE. Height (without shoes) is measured at Screening only.

4 ECOG Performance Status will be performed at the Screening, C1D1, C2D1, EOT and at 30-Day-Follow-Up visit. ECOG will be scored using the scale index in Appendix 6
5 C1D1 Vital Signs will be taken within 15 min pre-GS-5829 dose and 2 and 4 hours post dose (+/- 15 min); vital signs will be taken pre-dose only at all subsequent visits.
6 Triplicate ECG will be collected at any time during Screening window, C1D1, Day 1 of Cycles 2-6 (at pre-dose), and at EOT. In the Phase 1b Dose Escalation phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, and 8 hours post dose (+/- 20 min). In the Randomized Phase 2 Dose Expansion phase of the study, triplicate ECGs will be collected on C1D1 at pre-dose and 1-4 hrs post-dose and on C1D15 at pre-dose, 1 hour, 2 hours, 4 hours, and 6 hours post dose
(+/- 20 min). ECGs should always be collected prior to PK (or any other blood draw) if they are to be collected at the same nominal time point. Subjects should be resting quietly and free of distraction (eg, TV, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each time point.
7 Echocardiogram will be performed at screening, C2D1 and EOT. MUGA is acceptable. The same modality must be used throughout study participation.
8 Day 1 pre GS-5829 lab samples may be drawn up to two days prior to the Day 1 visit.
9 For Phase 1b Dose Escalation subjects, the 30-Day Safety Follow-Up will be the final study visit. Randomized Phase 2 Dose Expansion subjects will complete the 30-Day Safety Follow-Up Visit and proceed to Long Term Survival Follow-Up.
10 LTFU will begin for subjects participating in the Randomized Phase 2 Dose Expansion phase of the study after the 30 day Safety Follow Up visit for up to 2 years after the last dose of IP. A phone call will be made every 3 months to confirm whether subject has had disease progression.
11 AE reporting period begins once the Informed Consent Form has been signed. AEs will be assessed using NCI CTCAE (v 4.03) criteria at pre- and post-GS-5829 dosing during applicable clinic visits. Subjects will also return to clinic at 30-day post last IP dose to assess AEs and SAEs.
12 Beginning on C1D1, subjects will receive GS-5829 daily.
13 Subjects assigned to receive exemestane in combination with GS-5829 in the study will self-administer exemestane orally once daily starting on or before on C1D1 and thereafter at approximately the same time each day until the end of treatment. Subjects assigned to receive fulvestrant in combination with GS-5829 in this study will receive fulvestrant 500 mg IM on C1D1 and every 28 days (+/- 3 days) until the end of treatment. For subjects initiating fulvestrant on this study a single dose of fulvestrant 500 mg should be administered on Cycle 1 Day 15 (+/- 3 days).
14 Subject should use dosing diary daily and bring to cycle visit days.
15 Screening chemistry, hematology, coagulation are to be collected within 7 days of C1D1 for central lab assessment.
16 Coagulation assessment includes PT/INR, aPTT to be done at Screening and predose of: C1D1, C1D15 and C2D1
17 Serum pregnancy, Serum estradiol and FSH will be conducted at Screening, and EOT for all subjects. In addition, for subjects on goserelin, serum estradiol and FSH will be checked monthly on CXD1
18 HCV RNA Reflex is required
19 If available, paraffin embedded archival tumor tissue block or freshly sectioned unstained slides will be requested to be shipped to Gilead or designee. These samples will be requested prior to C1D1.
20 Tumor burden as assessed by RECIST v. 1.1 Guidelines
21 Tumor evaluation by CT/MRI or applicable scan will be performed during screening (within 8 weeks of C1D1) and every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of randomization. The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT/MRI to be done at EOT visit if not done within the previous 4 weeks.
22 Subjects will also undergo a bone scan during Screening and every 8 weeks (±7 days) for the first year and then every 12 weeks (±7 days) from the date of randomization. Scans at the EOT visit are not necessary if the prior scan was performed within 4 weeks prior to the EOT visit date.


PPD
PPD

Appendix 3. Pharmacokinetics, Pharmacodynamic Time Point Collection Tables

Phase 1b Dose Escalation[1]

Time point in hours from GS-5829 dose	Screening	C1D1	C1D15	C2D1	C3D1 and every 4 weeks [2]	EOT
Pre-dose		X	X			
0.5 Post-dose		X	X			
1 Post-dose		X	X			
2 Post-dose		X	X			
3 Post-dose		X	X	X	X	
4 Post-dose		X	X			
6 Post-dose		X	X			
8 Post-dose		X	X			
24 Post-dose		X	X			

1 PK and PD samples for GS-5829 will be collected on Day 1 and Day 15 of Cycle 1 at pre-dose 0.5, 1, 2, 3, 4, 6, 8 and 24 hours post-dose and anytime on Day 1 of Cycles 2 through 6

2 The last PK/PD collection will be at C6D1

Randomized Phase 2 Dose Expansion [1]

Time point in hours from GS-5829 dose[2]	Screening	C1D1	C1D15	C2D1	C2D15	C3D1	C6D1	EOT
Pre-dose		X	X			X	X	
1-4 Post-dose		X	X					

1 Sparse PK and PD samples will be collected at pre-dose and between 1 to 4 hours post-dose on Day 1 and Day 15 of Cycle 1 at pre-dose on Day 1 of Cycles 3 and 6. End PK/PD collection at C6D1

2 PK samples will only be collected for subjects who are randomized to a GS-5829 combination arm

Appendix 4. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v 4.03 can be assessed from the link below:

http://www.hrc.govt.nz/sites/default/files/CTCAE%20manual%20-%20DMCC.pdf

Appendix 5. Pregnancy Precautions, Definition for Female of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born subject is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Subjects with breast cancer who are also receiving hormonal therapies, women are considered to be in a postmenopausal state when they are ≥ 60 years of age with cessation of previously occurring menses for ≥ 12 months without an alternative cause. In addition, women of any age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their follicle stimulating hormone (FSH) level is in the postmenopausal range and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female subject of any age.

In addition, pre/perimenopausal women are considered in a postmenopausal state due to treatment with the LHRH agonist goserelin. Subjects must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug, leading to a reduction in luteinizing hormone production and consequent reduction of sex steroid hormones to castration levels by the time of exposure to study drugs.

b. Definition of Male Fertility

For the purposes of this study, a partner of a female study subject is considered to be fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

2) Contraception Requirements for Female Subjects

a. Study Drug Effects on Pregnancy and Hormonal Contraception

GS-5829 is contraindicated in pregnancy as any potential for human teratogenicity/fetotoxicity in early pregnancy is currently unknown. GS-5829 has insufficient data to exclude the possibility of a clinically relevant interaction with hormonal contraception that results in reduced contraception efficacy. Therefore, contraceptive steroids are not recommended as a contraceptive method either solely or as a part of a contraceptive regimen. Please refer to the latest version of the investigator's brochure for additional information.

b. Contraception Requirements for Female Subjects of Childbearing Potential

The inclusion of female subjects who are pre/peri-menopausal and treated with goserelin or an alternative LHRH agonist starting at least 4 weeks prior to first dose of study drug and throughout the duration of the study (per the above definition) of childbearing potential requires the use of highly effective contraceptive measures. They must also not rely on hormone-containing contraceptives as a form of birth control during the study. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to initial randomization. Pregnancy tests will be performed at protocol-specified dates thereafter. Female subjects must agree to one of the following from Screening until 30 days following the end of relevant systemic exposure.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the subject's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.

  — Intrauterine device (IUD) with a failure rate of <1% per year

  — Tubal sterilization

  — Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Subjects must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Unacceptable Birth Control Methods

Birth control methods that are unacceptable include periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the investigator if they become pregnant at any time during the study, or if they become pregnant within 30 days of last study drug dose. Subjects who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately. Subjects whose partner has become pregnant or suspects she is pregnant during the study must report the information to the investigator. Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 7.6.2.1.

Appendix 6. Performance Status Scoring System (ECOG)

Grade	ECOG
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, eg, light house work, 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

Appendix 7. RECIST 1.1

E.A. Eisenhauer[a, et al.] New response evaluation criteria in solid tumors:

Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228-247.

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New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

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ABSTRACT

Background: Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics: both tumour shrinkage (objective response) and disease progression are useful endpoints in clinical trials. Since RECIST was published in 2000, many investigators, cooperative groups, industry and government authorities have adopted these criteria in the assessment of treatment outcomes. However, a number of questions and issues have arisen which have led to the development of a revised RECIST guideline (version 1.1). Evidence for changes, summarised in separate papers in this special issue, has come from assessment of a large data warehouse (>6500 patients), simulation studies and literature reviews.

Highlights of revised RECIST 1.1: Major changes include: *Number of lesions to be assessed:* based on evidence from numerous trial databases merged into a data warehouse for analysis pur poses, the number of lesions required to assess tumour burden for response determination has been reduced from a maximum of 10 to a maximum of five total (and from five to two per organ, maximum). *Assessment of pathological lymph* nodes is now incorporated: nodes with a *short* axis of ⩾15 mm are considered measurable and assessable as target lesions. The short axis measurement should be included in the sum of lesions in calculation of tumour response. Nodes that shrink to <10 mm short axis are considered normal. *Confirma tion of response* is required for trials with response primary endpoint but is no longer required in randomised studies since the control arm serves as appropriate means of inter pretation of data. *Disease progression* is clarified in several aspects: in addition to the previ ous definition of progression in target disease of 20% increase in sum, a 5 mm absolute increase is now required as well to guard against over calling PD when the total sum is very

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small. Furthermore, there is guidance offered on what constitutes 'unequivocal progres sion' of non measurable/non target disease, a source of confusion in the original RECIST guideline. Finally, a section on detection of new lesions, including the interpretation of FDG PET scan assessment is included. *Imaging guidance*: the revised RECIST includes a new imaging appendix with updated recommendations on the optimal anatomical assess ment of lesions.

Future work: A key question considered by the RECIST Working Group in developing RECIST 1.1 was whether it was appropriate to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment or to functional assessment with PET or MRI. It was concluded that, at present, there is not sufficient standardisation or evidence to abandon anatomical assessment of tumour burden. The only exception to this is in the use of FDG PET imaging as an adjunct to determination of progression. As is detailed in the final paper in this special issue, the use of these promising newer approaches requires appropriate clinical validation studies.

1. Background

1.1. History of RECIST criteria

Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapeutics. Both tumour shrinkage (objective response) and time to the devel opment of disease progression are important endpoints in cancer clinical trials. The use of tumour regression as the endpoint for phase II trials screening new agents for evi dence of anti tumour effect is supported by years of evi dence suggesting that, for many solid tumours, agents which produce tumour shrinkage in a proportion of patients have a reasonable (albeit imperfect) chance of subsequently demonstrating an improvement in overall survival or other time to event measures in randomised phase III studies (re viewed in [1 4]). At the current time objective response car ries with it a body of evidence greater than for any other biomarker supporting its utility as a measure of promising treatment effect in phase II screening trials. Furthermore, at both the phase II and phase III stage of drug development, clinical trials in advanced disease settings are increasingly utilising time to progression (or progression free survival) as an endpoint upon which efficacy conclusions are drawn, which is also based on anatomical measurement of tumour size.

However, both of these tumour endpoints, objective re sponse and time to disease progression, are useful only if based on widely accepted and readily applied standard crite ria based on anatomical tumour burden. In 1981 the World Health Organisation (WHO) first published tumour response criteria, mainly for use in trials where tumour response was the primary endpoint. The WHO criteria introduced the con cept of an overall assessment of tumour burden by summing the products of bidimensional lesion measurements and determined response to therapy by evaluation of change from baseline while on treatment.[5] However, in the decades that followed their publication, cooperative groups and pharma ceutical companies that used the WHO criteria often 'modi fied' them to accommodate new technologies or to address areas that were unclear in the original document. This led to confusion in interpretation of trial results[6] and in fact, the application of varying response criteria was shown to lead to very different conclusions about the efficacy of the same regimen.[7] In response to these problems, an International Working Party was formed in the mid 1990s to standardise and simplify response criteria. New criteria, known as RECIST (Response Evaluation Criteria in Solid Tumours), were pub lished in 2000.[8] Key features of the original RECIST include definitions of minimum size of measurable lesions, instruc tions on how many lesions to follow (up to 10; a maximum five per organ site), and the use of unidimensional, rather than bidimensional, measures for overall evaluation of tu mour burden. These criteria have subsequently been widely adopted by academic institutions, cooperative groups, and industry for trials where the primary endpoints are objective response or progression. In addition, regulatory authorities accept RECIST as an appropriate guideline for these assessments.

1.2. Why update RECIST?

Since RECIST was published in 2000, many investigators have confirmed in prospective analyses the validity of substituting unidimensional for bidimensional (and even three dimen sional) based criteria (reviewed in [9]). With rare exceptions (e.g. mesothelioma), the use of unidimensional criteria seems to perform well in solid tumour phase II studies.

However, a number of questions and issues have arisen which merit answers and further clarity. Amongst these are whether fewer than 10 lesions can be assessed without affecting the overall assigned response for patients (or the conclusion about activity in trials); how to apply RECIST in randomised phase III trials where progression, not response, is the primary endpoint particularly if not all patients have measurable disease; whether or how to utilise newer imag ing technologies such as FDG PET and MRI; how to handle assessment of lymph nodes; whether response confirmation is truly needed; and, not least, the applicability of RECIST in trials of targeted non cytotoxic drugs. This revision of the RECIST guidelines includes updates that touch on all these points.

1.3. *Process of RECIST 1.1 development*

The RECIST Working Group, consisting of clinicians with expertise in early drug development from academic research organisations, government and industry, together with imaging specialists and statisticians, has met regularly to set the agenda for an update to RECIST, determine the evidence needed to justify the various changes made, and to review emerging evidence. A critical aspect of the revision process was to create a database of prospectively documented solid tumour measurement data obtained from industry and academic group trials. This database, assembled at the EORTC Data Centre under the leadership of Jan Bogaerts and Patrick Therasse (co authors of this guideline), consists of >6500 patients with >18,000 target lesions and was utilised to investigate the impact of a variety of questions (e.g. number of target lesions required, the need for response confirmation, and lymph node measurement rules) on response and progression free survival outcomes. The results of this work, which after evaluation by the RECIST Working Group led to most of the changes in this revised guideline, are reported in detail in a separate paper in this special issue.[10] Larry Schwartz and Robert Ford (also co authors of this guideline) also provided key databases from which inferences have been made that inform these revisions.[11]

The publication of this revised guideline is believed to be timely since it incorporates changes to simplify, optimise and standardise the assessment of tumour burden in clinical trials. A summary of key changes is found in Appendix I. Because the fundamental approach to assessment remains grounded in the anatomical, rather than functional, assessment of disease, we have elected to name this version RECIST 1.1, rather than 2.0.

1.4. *What about volumetric or functional assessment?*

This raises the question, frequently posed, about whether it is 'time' to move from anatomic unidimensional assessment of tumour burden to either volumetric anatomical assessment *or* to functional assessment (e.g. dynamic contrast enhanced MRI or CT or (18)F fluorodeoxyglucose positron emission tomographic (FDG PET) techniques assessing tumour metabolism). As can be seen, the Working Group and particularly those involved in imaging research, did not believe that there is at present sufficient standardisation and widespread availability to recommend adoption of these alternative assessment methods. The only exception to this is in the use of FDG PET imaging as an adjunct to determination of progression, as described later in this guideline. As detailed in paper in this special issue[12], we believe that the use of these promising newer approaches (which could either *add to* or *substitute for* anatomical assessment as described in RECIST) requires appropriate and rigorous clinical validation studies. This paper by Sargent et al. illustrates the type of data that will be needed to be able to define 'endpoints' for these modalities and how to determine where and when such criteria/modalities can be used to improve the reliability with which truly active new agents are identified and truly inactive new agents are discarded in comparison to RECIST criteria in phase II screening trials. The RECIST Working Group looks forward to such data emerging in the next few years to allow the appropriate changes to the next iteration of the RECIST criteria.

2. Purpose of this guideline

This guideline describes a standard approach to solid tumour measurement and definitions for objective assessment of change in tumour size for use in adult and paediatric cancer clinical trials. It is expected these criteria will be useful in all trials where objective response is the primary study endpoint, as well as in trials where assessment of stable disease, tumour progression or time to progression analyses are undertaken, since all of these outcome measures are based on an assessment of anatomical tumour burden and its change on study. There are no assumptions in this paper about the proportion of patients meeting the criteria for any of these endpoints which will signal that an agent or treatment regimen is active: those definitions are dependent on type of cancer in which a trial is being undertaken and the specific agent(s) under study. Protocols must include appropriate statistical sections which define the efficacy parameters upon which the trial sample size and decision criteria are based. In addition to providing definitions and criteria for assessment of tumour response, this guideline also makes recommendations regarding standard reporting of the results of trials that utilise tumour response as an endpoint.

While these guidelines may be applied in malignant brain tumour studies, there are also separate criteria published for response assessment in that setting.[13] This guideline is *not* intended for use for studies of malignant lymphoma since international guidelines for response assessment in lymphoma are published separately.[14]

Finally, many oncologists in their daily clinical practice follow their patients' malignant disease by means of repeated imaging studies and make decisions about continued therapy on the basis of both objective and symptomatic criteria. It is not intended that these RECIST guidelines play a role in that decision making, except if determined appropriate by the treating oncologist.

3. Measurability of tumour at baseline

3.1. *Definitions*

At baseline, tumour lesions/lymph nodes will be categorised measurable or non measurable as follows:

3.1.1. *Measurable*

Tumour 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 CT scan (CT scan slice thickness no greater than 5 mm; see Appendix II on imaging guidance).
- 10 mm caliper measurement by clinical exam (lesions which 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 *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 Schwartz et al. in this Special Issue[15]). See also notes below on 'Baseline documentation of target and non target lesions' for information on lymph node measurement.

3.1.2. *Non-measurable*

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ⩾10 to <15 mm short axis) as well as truly 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, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

3.1.3. *Special considerations regarding lesion measurability*

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:.

- Bone scan, 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 as 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 as malignant lesions (neither measurable nor non measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as 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:

- Tumour 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.

3.2. *Specifications by methods of measurements*

3.2.1. *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.

3.2.2. *Method of assessment*

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ⩾10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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. See Appendix II for more details.

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 based on the assumption that CT slice thickness is 5 mm or less. As is described in Appendix II, 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 in certain situations (e.g. for body scans). More details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next (described in greater detail in Appendix II). If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumour markers: Tumour markers *alone* cannot be used to assess *objective* tumour response. If markers are initially above

the upper normal limit, however, they must normalise for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA 125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published.[16–18] In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumour assessment for use in first line trials in ovarian cancer.[19]

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

4. Tumour response evaluation

4.1. *Assessment of overall tumour burden and measurable disease*

To assess objective response or future progression, it is necessary to estimate the *overall tumour burden at baseline* and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 3). In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non measurable disease only are also eligible.

4.2. *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 and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts et al.[10].

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. To illustrate this point see the example in Fig. 3 of Appendix II.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. As noted in Section 3, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of $\geqslant$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 tumour. 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, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which 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 (See also the example in Fig. 4 in Appendix II). All other pathological nodes (those with short axis $\geqslant$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.

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 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 diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.

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 are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

4.3. *Response criteria*

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

4.3.1. *Evaluation of target lesions*

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

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum 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* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* 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 diameters while on study.

4.3.2. 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 below 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 complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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 which 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 case report form. 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 (*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). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. As noted in Appendix II, 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'.

4.3.3. Evaluation of non-target lesions

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

Complete Response (CR): Disappearance of all non target lesions and normalisation of tumour 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 maintenance of tumour marker level above the normal limits.

Progressive Disease (PD): *Unequivocal progression* (see comments below) of existing non target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

4.3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non target disease requires additional explanation as follows:

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 such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy (see examples in Appendix II and further details below). A modest 'increase' in the size of one or more non target lesions is usually not sufficient to quality 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: i.e. an increase in tumour burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic

disease from localised to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. Some illustrative examples are shown in Figs. 5 and 6 in Appendix II. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

4.3.5. *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: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. 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 on a follow up study in an anatomical location that was *not* scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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.

While FDG PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:

a. Negative FDG PET at baseline, with a positive[1] FDG PET at follow up is a sign of PD based on a new lesion.
b. No FDG PET at baseline and a positive FDG PET at follow up:
   If the positive FDG PET at follow up corresponds to a new site of disease confirmed by CT, this is PD.
   If the positive FDG PET at follow up is not confirmed as a new site of disease on CT, additional follow up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG PET scan).
   If the positive FDG PET at follow up corresponds to a pre existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[1] A 'positive' FDG PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

4.4. *Evaluation of best overall response*

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (see Section 4.6). Specifically, in non randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.4.1. *Time point response*

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

When patients have non measurable (therefore non target) disease only, Table 2 is to be used.

4.4.2. *Missing assessments and inevaluable designation*

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point 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 at follow up 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.

4.4.3. *Best overall response: all time points*

The *best overall response* is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow up after the first SD assessment would be considered inevaluable.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non CR/non PD	No	PR
CR	Not evaluated	No	PR
PR	Non PD or not all evaluated	No	PR
SD	Non PD or not all evaluated	No	SD
Not all evaluated	Non PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non target lesions	New lesions	Overall response
CR	No	CR
Non CR/non PD	No	Non CR/non PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non CR/non PD' is preferred over 'stable disease' for non target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

4.4.4. *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 case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR NE PR as a confirmed response.

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 Tables 1 3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

a If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether 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 time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

needle aspirate/biopsy) before assigning a status of complete response. FDG PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG PET in this circumstance should be prospectively described in the protocol and supported by dis ease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG PET and biopsy res olution/sensitivity.

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.

4.5. *Frequency of tumour re-evaluation*

Frequency of tumour re evaluation while on treatment should be protocol specific and adapted to the type and sche dule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow up every 6 8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The proto col should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with meta static disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non target sites are evaluated at each assessment. In selected circum stances certain non target organs may be evaluated less fre quently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tu mour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease free survival, progression free survival) is the main endpoint of the study, then routine scheduled re evaluation of protocol specified sites of disease is warranted. In randomised com parative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6 8 weeks on treatment or every 3 4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

4.6. *Confirmatory measurement/duration of response*

4.6.1. *Confirmation*

In non randomised trials where response is the primary end point, confirmation of PR and CR is required to ensure re sponses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see the paper by Bogaerts et al. in this Special Issue[10]). However, in all other circum stances, i.e. in randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add va lue to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in partic ular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 8 weeks) that is defined in the study protocol.

4.6.2. *Duration of overall response*

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive dis ease is objectively documented (taking as reference for progres sive disease the smallest measurements recorded on study).

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

4.6.3. *Duration of stable disease*

Stable disease is measured from the start of the treatment (in randomised trials, from date of randomisation) until the crite ria for progression are met, taking as reference the *smallest sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease var ies in different studies and diseases. If the proportion of pa tients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression free survival are influenced by the frequency of follow up after baseline evaluation. It is not in the scope of this guideline to define a standard follow up frequency. The fre quency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if compari sons between trials are to be made.

4.7. *Progression-free survival/proportion progression-free*

4.7.1. *Phase II trials*

This guideline is focused primarily on the use of objective re sponse endpoints for phase II trials. In some circumstances, 're sponse rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression free survival' (PFS) or the 'proportion pro gression free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an appar ently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilising these endpoints are best designed with a randomised control. Exceptions may exist

where the behaviour patterns of certain cancers are so consis tent (and usually consistently poor), that a non randomised trial is justifiable (see for example van Glabbeke et al.[20]). How ever, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progres sion free in the absence of a treatment effect.

4.7.2. *Phase III trials*

Phase III trials in advanced cancers are increasingly designed to evaluate progression free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all pa tients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalisable if, in the disease under study, a substantial proportion of pa tients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, tri als allow entry of both patients with measurable disease as well as those with non measurable disease only. In this cir cumstance, care must be taken to explicitly describe the find ings which would qualify for progressive disease for those patients *without* measurable lesions. Furthermore, in this set ting, protocols must indicate if the maximum number of re corded target lesions for those patients with measurable disease may be relaxed from five to three (based on the data found in Bogaerts et al.[10] and Moskowitz et al.[11]). As found in the 'special notes on assessment of progression', these guide lines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumour mar ker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of pro gression. Centralised blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug ap proval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same. The article by Dancey et al. in this special issue[21] provides a more detailed discussion of the assessment of progression in randomised trials.

4.8. *Independent review of response and progression*

For trials where *objective response* (CR + PR) is the primary end point, and in particular where key drug development deci sions are based on the observation of a minimum number of responders, it is recommended that all claimed responses be reviewed by an expert(s) independent of the study. If the study is a randomised trial, ideally reviewers should be blinded to treatment assignment. Simultaneous review of the patients' files and radiological images is the best approach.

Independent review of progression presents some more complex issues: for example, there are statistical problems with the use of central review based progression time in place of investigator based progression time due to the poten tial introduction of informative censoring when the former precedes the latter. An overview of these factors and other lessons learned from independent review is provided in an article by Ford et al. in this special issue.[22]

4.9. *Reporting best response results*

4.9.1. *Phase II trials*

When response is the primary endpoint, and thus all patients must have measurable disease to enter the trial, all patients included in the study must be accounted for in the report of the results, even if there are major protocol treatment devia tions or if they are not evaluable. Each patient will be assigned one of the following categories:

1. Complete response
2. Partial response
3. Stable disease
4. Progression
5. Inevaluable for response: specify reasons (for example: early death, malignant disease; early death, toxicity; tumour assessments not repeated/incomplete; other (specify)).

Normally, all *eligible* patients should be included in the denominator for the calculation of the response rate for phase II trials (in some protocols it will be appropriate to include all treated patients). It is generally preferred that 95% two sided confidence limits are given for the calculated response rate. Trial conclusions should be based on the response rate for all eligible (or all treated) patients and should *not* be based on a selected 'evaluable' subset.

4.9.2. *Phase III trials*

Response evaluation in phase III trials may be an indicator of the relative anti tumour activity of the treatments eval uated and is almost always a secondary endpoint. Ob served differences in response rate may not predict the clinically relevant therapeutic benefit for the population studied. If objective response is selected as a primary end point for a phase III study (only in circumstances where a direct relationship between objective tumour response and a clinically relevant therapeutic benefit can be unambigu ously demonstrated for the population studied), the same criteria as those applying to phase II trials should be used and all patients entered should have at least one measur able lesion.

In those many cases where response is a secondary end point and not all trial patients have measurable disease, the method for reporting overall best response rates must be pre specified in the protocol. In practice, response rate may be reported using either an 'intent to treat' analysis (all ran domised patients in the denominator) or an analysis where only the subset of patients with measurable disease at baseline are included. The protocol should clearly specify how response results will be reported, including any subset analyses that are planned.

The original version of RECIST suggested that in phase III trials one could write protocols using a 'relaxed' interpreta tion of the RECIST guidelines (for example, reducing the num ber of lesions measured) but this should no longer be done since these revised guidelines have been amended in such a way that it is clear how these criteria should be applied for all trials in which anatomical assessment of tumour response or progression are endpoints.

Appendix I. Summary of major changes RECIST 1.0 to RECIST 1.1

	RECIST 1.0	RECIST 1.1	Rationale	Reference in special issue (if applicable)
Minimum size measurable lesions	CT: 10 mm spiral 20 mm non spiral	CT 10 mm; delete reference to spiral scan	Most scans used have 5 mm or less slice thickness Clearer to give instruction based on slice interval if it is greater than 5 mm	
	Clinical: 20 mm	Clinical: 10 mm (must be measurable with calipers)	Caliper measurement will make this reliable	
	Lymph node: not mentioned	CT: ⩾15 mm short axis for target ⩾10 <15 mm for non target <10 mm is non pathological	Since nodes are normal structure need to define pathological enlargement. Short axis is most sensitive	Schwartz et al.[15]
Special considerations on lesion measurability		Notes included on bone lesions, cystic lesions	Clarify frequently asked questions	
Overall tumour burden	10 lesions (5 per organ)	5 lesions (2 per organ)	Data warehouse analysis shows no loss of information if lesion number reduced from 10 to 5. A maximum of 2 lesions per organ yields sufficient representation per disease site	Bogaerts et al.[10]
Response criteria target disease	CR lymph node not mentioned	CR lymph nodes must be <10 mm short axis	In keeping with normal size of nodes	Schwartz et al.[15]
	PD 20% increase over smallest sum on study or new lesions	PD 20% increase over smallest sum on study (including baseline if that is smallest) and at least 5 mm increase or new lesions	Clarification that if baseline measurement is smaller than any on study measurement, it is reference against which PD is assessed 5 mm absolute increase to guard against over calling PD when total sum is very small and 20% increase is within measurement error	
Response criteria non target disease	'unequivocal progression' considered as PD	More detailed description of 'unequivocal progression' to indicate that it should not normally trump target disease status. It must be representative of overall disease status change, not a single lesion increase	Confusion with RECIST 1.0 where some were considering PD if 'increase' in any non target lesion, even when target disease is stable or responding	
New lesions		New section on New lesions	To provide guidance on when a lesion is considered new (and thus PD)	
Overall response	Table integrated target and non target lesions	Two tables: one integrating target and non target and the other of non target only	To account for the fact that RECIST criteria are now being used in trials where PFS is the endpoint and not all patients have measurable (target) disease at baseline	Dancey et al.[21]

		Special notes: How to assess and measure lymph nodes CR in face of residual tissue Discussion of 'equivocal' progression	Frequently asked questions on these topics	
Confirmatory measure	For CR and PR: criteria must be met again 4 weeks after initial documentation	Retain this requirement ONLY for non randomised trials with primary endpoint of response	Data warehouse shows that response rates rise when confirmation is eliminated, but the only circumstance where this is important is in trials where there is no concurrent comparative control and where this measure is the primary endpoint	Bogaerts et al.[10]
Progression free survival	General comments only	More specific comments on use of PFS (or proportion progression free) as phase II endpoint Greater detail on PFS assessment in phase III trials	Increasing use of PFS in phase III trials requires guidance on assessment of PD in patients with non measurable disease	Dancey et al.[21]
Reporting of response results	9 categories suggested for reporting phase II results	Divided into phase II and phase III 9 categories collapsed into 5 In phase III, guidance given about reporting response	Simplifies reporting and clarifies how to report phase II and III data consistently	
Response in phase III trials	More relaxed guidelines possible if protocol specified	This section removed and referenced in section above: no need to have different criteria for phase II and III	Simplification of response assessment by reducing number of lesions and eliminating need for confirmation in randomised studies where response is not the primary endpoint makes separate 'rules' unnecessary	
Imaging appendix	Appendix I	Appendix II: updated with detailed guidance on use of MRI, PET/CT Other practical guidance included	Evolving use of newer modalities addressed. Enhanced guidance in response to frequent questions and from radiology review experience	
New appendices		Appendix I: comparison of RECIST 1.0 and 1.1 Appendix III: frequently asked questions		

Conflict of interest statement

None declared.

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Appendix II. Specifications for standard anatomical radiological imaging

These protocols for image acquisition of computed tomography (CT) and magnetic resonance imaging (MRI) are recommendations intended for patients on clinical trials where RECIST assessment will be performed. Standardisation of imaging requirements and image acquisition parameters is ideal to allow for optimal comparability of subjects within a study and results between studies. These recommendations are designed to balance optimised image acquisition protocols with techniques that should be feasible to perform globally at imaging facilities in all types of radiology practices. These guidelines are not applicable to functional imaging techniques or volumetric assessment of tumour size.

Scanner quality control is highly recommended and should follow standard manufacturer and facility maintenance schedules using commercial phantoms. It is likely that for RECIST unidimensional measurements this will be adequate to produce reproducible measurements. Imaging quality control for CT includes an analysis of image noise and uniformity and CT number as well as spatial resolution. The frequency of quality control analysis is also variable and should focus on clinically relevant scanning parameters. Dose analysis is always important and the use of imaging should follow the ALARA principle, 'As Low As Reasonably Achievable', which refers to making every reasonable effort to maintain radiation exposures as far below the dose limits as possible.

Specific notes

Chest X ray measurement of lesions surrounded by pulmonary parenchyma is feasible, but not preferable as the measurement represents a summation of densities. Furthermore, there is poor identification of new lesions within the chest on X ray as compared with CT. Therefore, measurements of pulmonary parenchymal lesions as well as mediastinal disease are optimally performed with CT of the chest. MRI of the chest should only be performed in extenuating circumstances. Even if IV contrast cannot be administered (for example, in the situation of allergy to contrast), a non contrast CT of the chest is still preferred over MRI or chest X ray.

CT scans: CT scans of the chest, abdomen, and pelvis should be contiguous throughout all the anatomic region of interest. As a general rule, the minimum size of a measurable lesion at baseline should be no less than double the slice thickness and also have a minimum size of 10 mm (see below for minimum size when scanners have a slice thickness more than 5 mm). While the precise physics of lesion size and partial volume averaging is complex, lesions smaller than 10 mm may be difficult to accurately and reproducibly measure. While this rule is applicable to baseline scans, as lesions potentially decrease in size at follow up CT studies, they should still be measured. Lesions which are reported as 'too small to measure' should be assigned a default measurement of 5 mm if they are still visible.

The most critical CT image acquisition parameters for optimal tumour evaluation using RECIST are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval*.

a. *Anatomic coverage*: Optimal anatomic coverage for most solid tumours is the chest, abdomen and pelvis. Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and

should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as a new lesion representing disease progression, careful consid eration should be given to the extent of imaging coverage at baseline and at subsequent follow up time points. This will enable better consistency not only of tumour measurements but also identification of new disease.

b. *IV contrast administration*: Optimal visualisation and measurement of metastases in solid tumours requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. Typically, most abdomi nal imaging is performed during the portal venous phase and (optimally) about the same time frame after injection on each examination (see Fig. 1 for impact of different phase of IV contrast on lesion measurement). Most solid tumours may be scanned with a single phase after administration of contrast. While triphasic CT scans are sometimes performed on other types of vascular tumours to improve lesion conspicuity, for consistency and uniformity, we would recommend tri phasic CT for hepatocellular and neuroendocrine tumours for which this scanning protocol is generally standard of care, and the improved temporal resolution of the triphasic scan will enhance the radiologists' abil ity to consistently and reproducibly measure these lesions. The precise dose and rate of IV contrast is dependent upon the CT scanning equipment, CT acqui sition protocol, the type of contrast used, the available venous access and the medical condition of the patient. Therefore, the method of administration of intravenous contrast agents is variable. Rather than try to institute rigid rules regarding methods for administering contrast agents and the volume injected, it is appropriate to suggest that an adequate volume of a suitable contrast agent should be given so that the metastases are demonstrated to best effect and a *con sistent method* is used on subsequent examinations for any given patient (ideally, this would be specified in the protocol or for an institution). It is very important that the same technique be used at baseline and on fol low up examinations for a given patient. This will greatly enhance the reproducibility of the tumour mea surements. If prior to enrolment it is known a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non contrast CT or MRI (with or without IV contrast) should be used to evaluate the subject at baseline and follow up should be guided by the tumour type under investigation and the anatomic location of the disease. For patients who develop contraindica tions to contrast after baseline contrast CT is done, the decision as to whether non contrast CT or MRI (enhanced or non enhanced) should be performed should also be based on the tumour type, anatomic location of the disease and should be optimised to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions 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 (see Fig. 2 for a comparison of CT and MRI of the same lesion). Oral contrast is recommended to help visualise and differ entiate structures in the abdomen.

c. *Slice thickness and reconstruction interval*: RECIST measure ments may be performed at most clinically obtained slice thicknesses. It is recommended that CT scans be performed at 5 mm contiguous slice thickness or less and indeed this guideline presumes a minimum 5 mm thickness in recommendations for measurable lesion definition. Indeed, variations in slice thickness can have an impact on lesion measurement and on detection of new lesions. However, consideration should also be given for minimising radiation exposure. With these parameters, a minimum 10 mm lesion is considered measurable at baseline. Occasionally, institutions may perform medically acceptable scans at slice thicknesses *greater than* 5 mm. If this occurs, the minimum size of measurable lesions at baseline should be *twice the slice*

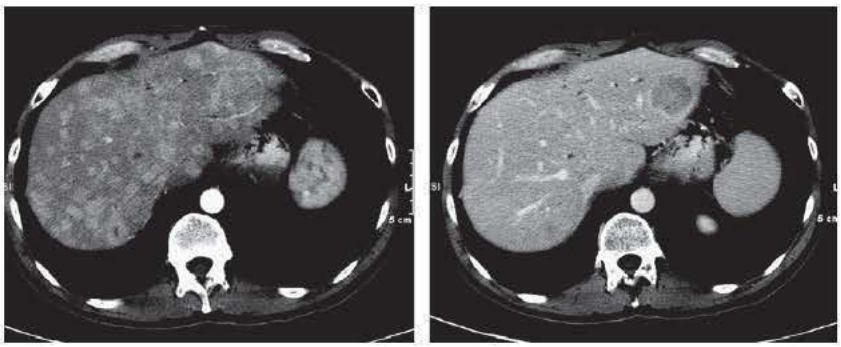

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration as does any potential lesion measurement. Consistent CT scan acquisition, including phase of contrast administration, is important for optimal and reproducible tumour

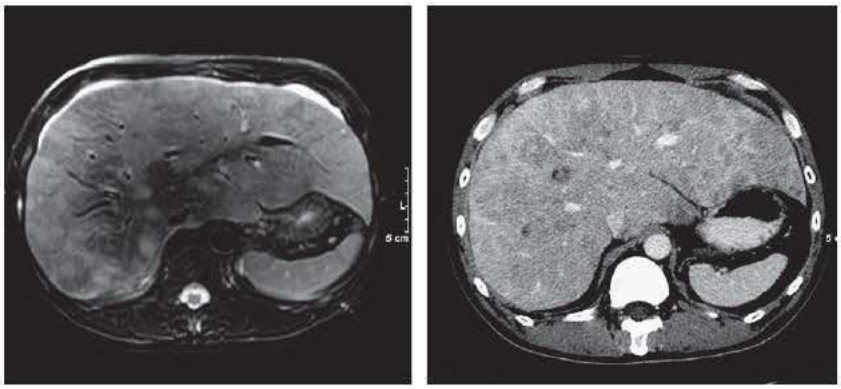

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

thickness of the baseline scans. Most contemporary CT scanners are multidetector which have many imaging options for these acquisition parameters.[23] The equip ment vendor and scanning manual should be reviewed if there are any specific system questions.

d. *Alternative contrast agents*: There are a number of other, new contrast agents, some organ specific.[24] They may be used as part of patient care for instance, in liver lesion assessment, or lymph node characterisation[25], but *should not as yet be used in clinical trials*.

FDG PET has gained acceptance as a valuable tool for detecting, staging and restaging several malignancies. Criteria for incorporating (or substituting) FDG PET into anatomical assessment of tumour response in phase II trials are not yet available, though much research is ongoing. Nevertheless, FDG PET is being used in many drug development trials both as a tool to assess therapeutic efficacy and also in assessment of progression. If FDG PET scans are included in a protocol, by consensus, an FDG uptake period of 60 min prior to imaging has been decided as the most appropriate for imaging of pa tients with malignancy.[26] Whole body acquisition is impor tant since this allows for sampling of all areas of interest and can assess if new lesions have appeared thus determining the possibility of interval progression of disease. Images from the base of the skull to the level of the mid thigh should be ob tained 60 min post injection. PET camera specifications are variable and manufacturer specific, so every attempt should be made to use the same scanner, or the same model scanner, for serial scans on the same patient. Whole body acquisitions can be performed in either 2 or 3 dimensional mode with attenuation correction, but the method chosen should be con sistent across all patients and serial scans in the clinical trial.

PET/CT scans: Combined modality scanning such as with PET CT is increasingly used in clinical care, and is a modal ity/technology that is in rapid evolution; therefore, the recom mendations in this paper may change rather quickly with time. At present, low dose or attenuation correction CT por tions of a combined PET CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic con trast enhanced CT scans for anatomically based RECIST mea surements. However, if a site can document that the CT performed as part of a PET CT is of identical diagnostic qual ity to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces addi tional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound examinations should not be used in clinical trials to measure tumour regression or progression of lesions be cause the examination is necessarily subjective and operator dependent. The reasons for this are several: Entire examina tions cannot be reproduced for independent review at a later date, and it must be assumed, whether or not it is the case, that the hard copy films available represent a true and accu rate reflection of events. Furthermore, if, for example, the only measurable lesion is in the para aortic region of the abdomen and if gas in the bowel overlies the lesion, the lesion will not be detected because the ultrasound beam cannot penetrate the gas. Accordingly, the disease staging (or restag ing for treatment evaluation) for this patient will not be accurate.

While evaluation of lesions by *physical examination* is also of limited reproducibility, it is permitted when lesions are superficial, at least 10 mm size, and can be assessed using calipers. In general, it is preferred if patients on clinical trials have at least one lesion that is measurable by CT. Other skin or palpable lesions may be measured on physical examina tion and be considered target lesions.

Use of *MRI* remains a complex issue. MRI has excellent contrast, spatial and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity and mea surement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimised for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. Generally, axial imaging of the abdomen and pelvis with T1 and T2 weighted imaging along with gadolinium enhanced imaging should be performed. The field of view, matrix, number of excitations, phase encode steps, use of fat sup pression and fast sequences should be optimised for the spe

cific body part being imaged as well as the scanner utilised. It is beyond the scope of this document or appendix to pre scribe specific MRI pulse sequence parameters for all scan ners, body parts and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath hold scanning tech niques if possible.

Selection of target lesions: In general, the *largest* lesions rep resentative of involved organs (up to a maximum of two per organ and five total) are selected to follow as target lesions. However, in some cases, the largest lesions may not be easily measured and are not suitable for follow up because of their configuration. In these cases, identification of the largest *most reproducible* lesions is advised. Fig. 3 provides an illustrative example where the largest lesion is not the most reproducible and another lesion is better to select and follow:

Measurement of lesions

The longest diameter of selected lesions should be measured in the plane in which the images were acquired. For body CT, this is the axial plane. In the event isotropic reconstructions are performed, measurements can be made on these recon structed images; however, it should be cautioned that not all radiology sites are capable of producing isotropic recon structions. This could lead to the undesirable situation of measurements in the axial plane at one assessment point and in a different plane at a subsequent assessment. There are some tumours, for instance paraspinal lesions, which are better measured in the coronal or sagittal plane. It would be acceptable to measure these lesions in these planes if the reconstructions in those planes were isotropic or the images were acquired with MRI in those planes. Using the same plane of evaluation, the maximal diameter of each target lesion should always be measured at subsequent follow up time points even if this results in measuring the lesion at a differ ent slice level or in a different orientation or vector compared with the baseline study. Software tools that calculate the maximal diameter for a perimeter of a tumour may be em ployed and may even reduce variability.

The only exception to the longest diameter rule is lymph node measurement. Because malignant nodes are identified by the length of their short axis, this is the guide used to determine not only whether they are pathological but is also the dimension measured for adding into the sum of target le sions. Fig. 4 illustrates this point: the large arrow identifies a malignant node: the shorter perpendicular axis is $\geqslant$15 mm and will be recorded. Close by (small arrow) there is a normal node: note here the long axis is greater than 10 mm but the short axis is well below 10 mm. This node should be consid ered non pathological.

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the pa tient's response at the point in time when the lesion reap pears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be consid ered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself en

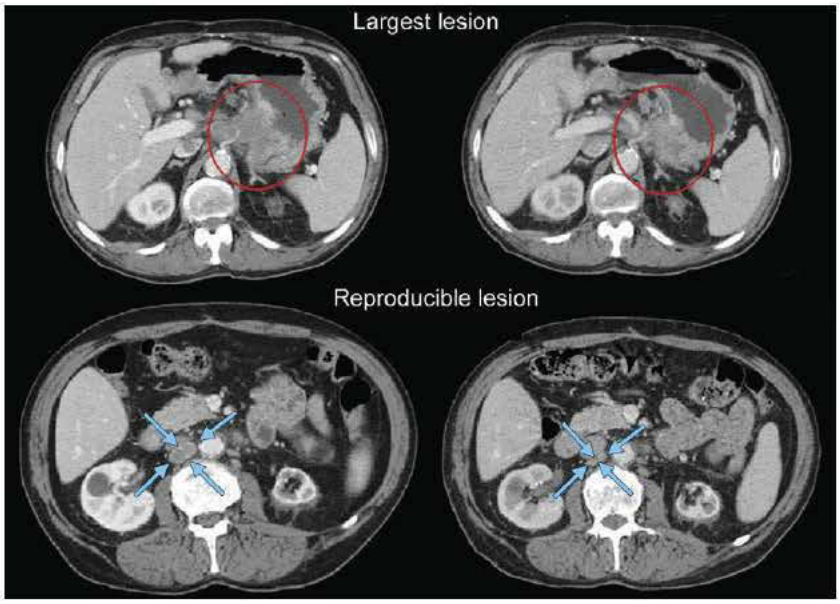

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention at baseline and follow-up. However, this is potentially challenging to reproduce in a multicentre trial and if attempted should be done with careful imaging input and analysis. The most reproducible lesion is a lymph node (circled at baseline and at follow-up in the bottom two images).

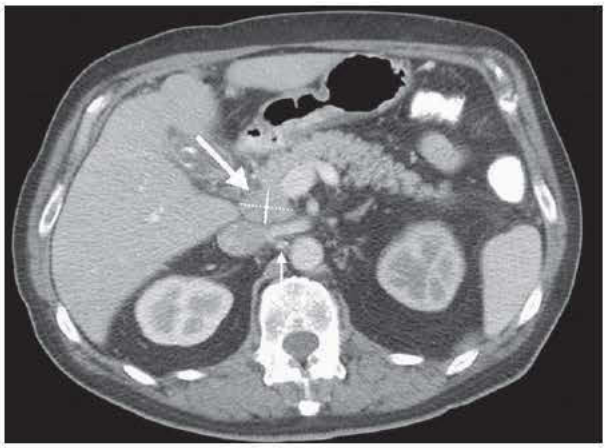

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually 'disappear' but are not visualised because they are beyond the resolving power of the imaging modality employed.

The identification of the precise boundary definition of a lesion may be difficult especially when the lesion is embedded in an organ with a similar contrast such as the liver, pancreas, kidney, adrenal or spleen. Additionally, peritumoural oedema may surround a lesion and may be difficult to distinguish on certain modalities between this oedema and actual tumour. In fact, pathologically, the presence of tumour cells within the oedema region is variable. Therefore, it is most critical that the measurements be obtained in a reproducible manner from baseline and all subsequent follow up time points. This is also a strong reason to consistently utilise the same imaging modality.

When lesions 'fragment', the individual lesion diameters 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 'merged lesion'.

Progression of non-target lesions

To achieve 'unequivocal progression' there must be an *overall* level of substantial worsening in non target disease that is of a magnitude that, even in the presence of SD or PR in target disease, the treating physician would feel it important to change therapy. Examples of unequivocal progression are shown in Figs. 5 and 6.

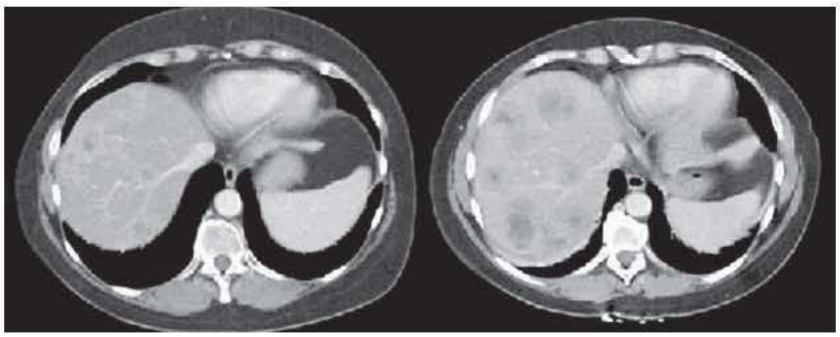

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

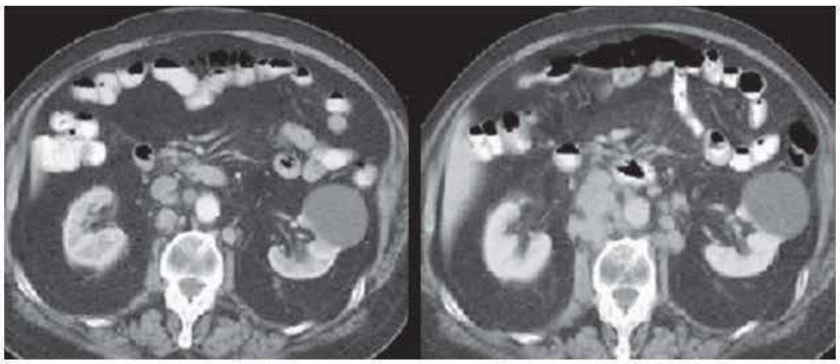

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

Appendix III. Frequently asked questions

Question	Answer
What should be done if several unique lesions at baseline become confluent at a follow up evaluation?	Measure the longest diameter of the confluent mass and record to add into the sum of the longest diameters
How large does a new lesion have to be to count as progression? Does any small subcentimetre lesion qualify, or should the lesion be at least measurable?	New lesions do not need to meet 'measurability criteria' to be considered valid. If it is clear on previous images (with the same technique) that a lesion was absent then its definitive appearance implies progression. If there is any doubt (because of the techniques or conditions) then it is suggested that treatment continue until next scheduled assessment when, generally, all should be clear. Either it gets bigger and the date of progression is the date of the first suspicion, or it disappears and one may then consider it an artefact with the support of the radiologists
How should one lesion be measured if on subsequent exams it is split into two?	Measure the longest diameter of each lesion and add this into the sum
Does the definition of progression depend on the status of all target lesions or only one?	As per the RECIST 1.1 guideline, progression requires a 20% increase in the sum of diameters of all target lesions AND a minimum absolute increase of 5 mm in the sum
Are RECIST criteria accepted by regulatory agencies?	Many cooperative groups and members of pharma were involved in preparing RECIST 1.0 and have adopted them. The FDA was consulted in their development and supports their use, though they don't require it. The European and Canadian regulatory authorities also participated and the RECIST criteria are now integrated in the European note for guidance for the development of anticancer agents. Many pharmaceutical companies are also using them. RECIST 1.1 was similarly widely distributed before publication
What is the criterion for a measurable lesion if the CT slice thickness is >5 mm?	RECIST 1.1 recommends that CT scans have a maximum slice thickness of 5 mm and the minimum size for a measurable lesion is twice that: 10 mm (even if slice thickness is <5 mm). If scanners with slice thickness >5 mm are used, the minimum lesion size must have a longest diameter twice the actual slice thickness
What should we record when target lesions become so small they are below the 10 mm 'measurable' size?	Target lesion measurability is defined at baseline. Thereafter, actual measurements, even if <10 mm, should be recorded. If lesions become very small, some radiologists indicate they are 'too small to measure'. This guideline advises that when this occurs, if the lesion is actually still present, a default measurement of 5 mm should be applied. If in fact the radiologist believes the lesion has gone, a default measurement of 0 mm should be recorded
If a patient has several lesions which have decreased in size to meet PR criteria and one has actually disappeared, does that patient have PD if the 'disappeared' lesion reappears?	Unless the sum meets the PD criteria, the reappearance of a lesion in the setting of PR (or SD) is not PD. The lesion should simply be added into the sum. If the patients had had a CR, clearly reappearance of an absent lesion would qualify for PD
When measuring the longest diameter of target lesions in response to treatment, is the same axis that was used initially used subsequently, even if there is a shape change to the lesion that may have produced a new longest diameter?	The longest diameter of the lesion should always be measured even if the actual axis is different from the one used to measure the lesion initially (or at different time point during follow up) The only exception to this is lymph nodes: as per RECIST 1.1 the short axis should always be followed and as in the case of target lesions, the vector of the short axis may change on follow up
Target lesions have been selected at baseline and followed but then one of these target lesions then becomes non evaluable (i.e. different technique used) What is the effect this has on the other target lesions and the overall response?	What may be done in such cases is one of the following: (a) If the patient is still being treated, call the centre to be sure that future evaluations are done with the baseline technique so at least SOME courses are fully evaluable (b) If that is not possible, check if there IS a baseline exam by the same technique which was used to follow patients…in which case if you retrieve the baseline measures from that technique you retrieve the lesion evaluability (c) If neither (a) nor (b) is possible then it is a judgement call about whether you delete the lesion from all forms or consider the impact of the lesion overall is so important that its being non evaluable makes the overall response interpretation inevaluable without it. Such a decision should be discussed in a review panel It is NOT recommended that the lesion be included in baseline sums and then excluded from follow up sums since this biases in favour of a response

(*continued on next page*)

Appendix III – *continued*

Question	Answer
What if a single non target lesion cannot be reviewed, for whatever reason; does this negate the overall assessment?	Sometimes the major contribution of a single non target lesion may be in the setting of CR having otherwise been achieved: failure to examine one non target in that setting will leave you unable to claim CR. It is also possible that the non target lesion has undergone such substantial progression that it would override the target disease and render patient PD. However, this is very unlikely, especially if the rest of the measurable disease is stable or responding
A patient has a 32% decrease in sum cycle 2, a 28% decrease cycle 4 and a 33% decrease cycle 6. Does confirmation of PR have to take place in sequential scans or is a case like this confirmed PR?	It is not infrequent that tumour shrinkage hovers around the 30% mark. In this case, most would consider PR to have been confirmed looking at this overall case. Had there been two or three non PR observations between the two time point PR responses, the most conservative approach would be to consider this case SD
In the setting of a breast cancer neoadjuvant study, would mammography not be used to assess lesions? Is CT preferred in this setting?	Neither CT nor mammography are optimal in this setting. MRI is the preferred modality to follow breast lesions in a neoadjuvant setting
A patient has a lesion measurable by clinical exam and by CT scan. Which should be followed?	CT scan. Always follow by imaging if that option exists since it can be reviewed and verified
A lesion which was solid at baseline has become necrotic in the centre. How should this be measured?	The longest diameter of the entire lesion should be followed. Eventually, necrotic lesions which are responding to treatment decrease in size. In reporting the results of trials, you may wish to report on this phenomenon if it is seen frequently since some agents (e.g. angiogenesis inhibitors) may produce this effect
If I am going to use MRI to follow disease, what is minimum size for measurability?	MRI may be substituted for contrast enhanced CT for some sites, but not lung. The minimum size for measurability is the same as for CT (10 mm) as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness. In the event there are inter slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline
Can PET CT be used with RECIST?	At present, the low dose or attenuation correction CT portion of a combined PET CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if your site has documented that the CT performed as part of a PET CT is of the same diagnostic quality as a diagnostic CT (with IV and oral contrast) then the PET CT can be used for RECIST measurements. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed

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Appendix 8. Exemestane (Aromasin®) Prescribing Information

http://www.pfizer.com/products/product-detail/aromasin

Appendix 9. Fulvestrant (Faslodex®) Prescribing Information

http://www.faslodexhcp.com/home.html

Appendix 10. Bayesian Logistic Regression Model

Determination of the MTD will be based on the posterior probability of DLT rate estimated by a 2-parameter BLRM with overdose control (Neuenschwander et. al. 2008) and calculated using East software (East 6.3, Cytel Inc. 2014).

Let $\pi[d_i]$ be the probability of DLT at dose level d_i of GS-5829. The statistical model describing dose-toxicity relationship will have the following form:

$$\pi[d_i] = \frac{\exp(\log(\alpha) + \beta\log(\frac{d_i}{d^*}))}{1 + \exp(\log(\alpha) + \beta\log(\frac{d_i}{d^*}))}$$

where $\alpha, \beta > 0$ and d^* is the reference dose level. The prior specification of the model parameters is provided below. The estimate of parameters will be updated as data are accumulated and the toxicity probability at each dose level will be calculated based on the posterior distributions of the model parameters. The estimated posterior probability of DLT rate at each dose level will be summarized using the following intervals:

Under dosing: [0.00, 0.167)

Targeted toxicity: [0.167, 0.333]

Excessive toxicity: (0.333, 1.00]

The overdose control criterion is set as the posterior probability of excessive toxicity less than 25%. The dose level recommended for the next cohort will be the dose cohort at which the posterior probability for the target toxicity interval is maximum among all dose candidates satisfying the overdose control criterion.

Each trial can be stopped if any one of three criteria is met:

1. The posterior probability of targeted toxicity exceeds 70% and at least 6 subjects have been allocated at a dose level

2. Maximum number of subjects (N=12) has been treated at a dose level

3. Maximum number of subjects (N=30) has been reached

1. Planned Dose Levels

The provisional dose levels for GS-5829 are 2 mg, 3 mg, 4 mg, 6 mg and 9 mg once daily.

2. Prior Specification

The prior distribution for (log(α), log(β)) is assumed to be a bivariate normal distribution. The following non-informative prior is used first:

- The median DLT rate at 3 mg is assumed to be 15%, i.e. mean(log(α))= -1.73.
- A doubling in dose is assumed to double the odds of DLT, i.e. mean(log(β)) = 0
- The StD of log(α) is set to 2 and the StD of log(β) to 1.
- The correlation between log(α) and log(β) is set to be 0.

Then the posterior is calculated based on the data collected from other on-going studies (GS-US-350-1599 and GS-US-350-1604) and will be updated as more data in these studies are collected. The prior for the current study will be based on the posterior calculated based on the data from GS-US-350-1599 and GS-US-350-1604 with inflated variance to discount the information from GS-US-350-1599 and GS-US-350-1604 considering between-trial variations.

Appendix Table 1. DLT data collected in GS-US-350-1599 and GS-US-350-1604 as of 2 June 2016*

QD Dose (mg)	Total number of evaluable subjects	Number of subjects with DLT
0.6	1	0
1.4	1	0
2	5	0
3	6	1
4	2	1

* Current data were collected only for subjects with GS-5829 monotherapy

Appendix Table 2. Prior for and Posterior from current data collected in GS-US-350-1599 and GS-US-350-1604

Parameter	Means	Variances	Correlation
Prior for (log(α), log(β))	(-1.73, 0)	(4, 1)	0
Posterior for (log(α), log(β)) from data in Appendix Table 1	(-1.84, 0.49)	) (0.63, 0.93)	0.01
Prior for (log(α), log(β)) used to assess operating characteristics by simulation	(-1.84, 0.49)	(0.95, 1.40)	0.01

Appendix Table 3 shows the posterior probabilities of DLT rate based on current data from GS-US-1599 and GS-1604. Because there is a high chance of under dosing for 2 mg and low chance of overdosing for 3 mg, 3 mg once daily of GS-5829 is planned as the starting dose for both Group A and Group B in the Phase 1b Dose Escalation portion of this study**.** The starting dose level may be either higher or lower than 3 mg once daily, if either a higher or lower dose has been demonstrated to be both safe and tolerable in Studies GS-US-350-1599 and GS-US-250-1604. The new dose level will be selected prior to initiating dosing in this study.

Appendix Table 3. Summary of posterior probabilities of DLT based on data from GS-US-350-1599 and GS-US-350-1604 as of 2 June 2016

QD Dose (mg)	Pr(DLT)	Prior Probability of		
	Median	Under [0%, 16.7%)	Target [16.7% 33.3%]	Excessive (33.3%, 100%)
2	0.07	0.87	0.12	0.01
3	0.12	0.51	0.44	0.05
4	0.23	0.29	0.40	0.31
6	0.40	0.15	0.24	0.61
9	0.58	0.09	0.20	0.71

3. Operating Characteristics

In order to assess operating characteristics, simulation was performed under 2 hypothetical scenarios using East software (East 6.3, Cytel Inc. 2014). A total of 1000 trials were simulated under each scenario.

Scenario 1: Only the lowest dose level (2 mg) is safe

Scenario 2: The dose level of 4 mg or below are safe

Appendix Table 4. True underlying DLT rates in hypothetical scenarios

QD Dose (mg)	True DLT rate	
	Scenario 1	Scenario 2
2	0.30	0.10
3	0.40	0.20
4	0.50	0.30
6	0.60	0.40
9	0.70	0.50

As shown in Appendix Table 5, the simulations illustrate that the model has reasonable operating characteristics. The probabilities of recommending a correct dose level and stopping the study with declaring all dose levels to be toxic are 37.2% and 48.6%, respectively, in Scenario 1. The probability of recommending a correct dose level in Scenario 2 is 72.3%.

Appendix Table 5. Simulation results for operating characteristics in hypothetical scenarios

Operating Characteristics	Scenario 1	Scenario 2
Proportion of trials that recommend dose levels with true Pr(DLT) in [0.167, 0.333] (Correct decision)	37.2%	72.3%
Proportion of trials that recommend dose levels with true Pr(DLT)>0.333 (Patient risk)	14.2%	2.9%
Proportion of trials that recommend dose levels with true Pr(DLT)<0.167	0	19.8%
Proportion of trials which stops early because all dose levels are too toxic	48.6%	5.0%
Average number of subjects evaluated	13	19