CLINICAL STUDY PROTOCOL

Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5829 as a Monotherapy in Subjects with Advanced Solid Tumors and Lymphomas and in Combination with Exemestane or Fulvestrant in Subjects with Estrogen Receptor Positive Breast Cancer	
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404	
IND Number:	124032	
EudraCT Number:	2016-001912-39	
Clinical Trials.gov Identifier:	NCT02392611	
Indication:	Solid tumors and lymphomas	
Protocol ID:	GS-US-350-1599	
Clinical Program Manager:	Name: Telephone: Email:	PPD PPD PPD
Gilead Medical Monitor:	Name: Telephone: Fax: Mobile: Email:	PPD PPD PPD PPD PPD
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TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

PROTOCOL SYNOPSIS

Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5829 as a Monotherapy in Subjects with Advanced Solid Tumors and Lymphomas and in Combination with Exemestane or Fulvestrant in Subjects with Estrogen Receptor Positive Breast Cancer
IND Number:	124032
EudraCT Number:	2016-001912-39
Clinical Trials.gov Identifier:	NCT02392611
Study Centers Planned:	Approximately 5 centers in the United States and approximately 10 centers in France
Objectives:	The primary objectives of this study are as follows: • Characterize the safety and tolerability of GS-5829 as a monotherapy in subjects with advanced solid tumors and lymphomas • Determine the maximum tolerated dose (MTD) or recommended dose for phase 2 (RDP2) of GS-5829 as a monotherapy in subjects with advanced solid tumors and lymphomas • Characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer • Determine the MTD or RDP2 of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer The secondary objective of this study is: • Evaluate the pharmacokinetics (PK) of GS-5829 alone in subjects with advanced solid tumors and lymphomas and in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer

CCI [redacted]

Study Design:

This is an open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, and PD of GS-5829 as a single agent in subjects with advanced solid tumors and lymphomas and in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer.

Group 1: Single agent GS-5829 in solid tumors and lymphomas

Cohorts of subjects with advanced solid tumors and lymphomas who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive oral GS-5829 as monotherapy once daily (QD). The starting dose will be 0.6 mg. Each dose level will enroll 1 subject until a ≥ Grade 2 treatment-related toxicity is observed within the initial dosing period (Study Day 1 through C1D28 for all cohorts). At Dose Level 5 or if a ≥ Grade 2 treatment-related toxicity is observed (whichever occurs first), the

dose level will be expanded to 3 subjects. (Note: subjects enrolled with Grade 2 hemoglobin [Hb] must have Hb worsen by at least 1 grade from baseline to be considered for expansion of the cohort to 3 subjects).

Once a dosing level has been expanded to 3 subjects, a standard 3+3 study design will begin and, dose escalation [3+3] will be performed at every subsequent dose level with cohort sizes of 3 to 6 subjects. Subjects in the first 3 cohorts will receive a single dose and then approximately

7 days later, initiate dosing once daily. Subjects will return to the clinic for frequent evaluation and monitoring as per Appendix 2.

The doses for each Dose Level are shown in the table below.

Group 1: Single Agent GS-5829

Dose Level	GS-5829*
1	0.6 mg
2	1.4 mg
3	2 mg
4	3 mg
5	4 mg
6	6 mg
7	9 mg
8	12 mg

* Dose Levels may be modified based on emerging safety and PK results.

If a dose limiting toxicity (DLT) occurs within the 28 day DLT period at any dose level, this level will be expanded to enroll 3 additional subjects.

The safety and tolerability of each dose level will be assessed by a safety review team (SRT) after all subjects in the cohort have been followed for at least 28 days after the first dose of GS-5829. If no DLTs occur in up to 3 subjects or < 2 DLTs occur in up to 6 subjects on any Dose Level after 28 days on treatment, the next Dose Level will open. Each subsequent Dose Level will open if the Dose Level preceding has no DLTs in 3 subjects or < 2 DLTs in up to 6 subjects.

Prior to initiating enrollment for Dose Level 4 in Group 1, an analysis of all available safety, PK, and PD data from previous cohorts will be reviewed.

If a subject is enrolled in a dose level but does not complete the PK or PD analysis, they may continue on study but an additional subject may be enrolled at that dose level.

The MTD is the highest dose level with a subject incidence of ≤ 1 DLTs during the first 28 days of study drug dosing of 6 subjects. A minimum of 6 subjects need to be treated at a dose level before this dose level can be deemed as the MTD.

Group 2: Combination therapy of GS-5829 with exemestane or fulvestrant in patients with advanced stage estrogen receptor positive breast cancer

Cohorts of subjects with advanced stage estrogen receptor positive breast cancer 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 full standard doses of exemestane or fulvestrant. The starting dose of GS-5829 will be 2.0 mg QD, which is a dose level that has been demonstrated to be safe and tolerable (no Grade 2 or higher drug related toxicity) as a single agent in patients with solid tumors. Dose escalation will continue with cohort sizes of 3-6 subjects in parallel arms: Group 2A will initiate with 2.0 mg of GS-5829 orally once daily on Cycle 1 Day 1 combined with 25 mg of exemestane administered once daily beginning on Cycle 1 Day 1. The subject may initiate exemestane any time prior to, or on, Cycle 1 Day 1. Group 2B will initiate with 2.0 mg of GS-5829 orally once daily on Cycle 1 Day 1 with 500 mg fulvestrant administered intramuscularly (Cycle 1 Day 1 and then every 28 days (+/-3 days). If Cycle 1 Day 1 is the subject's first dose of fulvestrant, a one-time additional dose of fulvestrant should be administered on Cycle 1 Day 15.

The candidate doses of GS-5829 for each Dose Level for Group 2 are shown in the table below.

Group 2: Combination of GS-5829 in Breast Cancer

Dose Level	GS-5829*	Group 2A Exemestane	Group 2B Fulvestrant
1	2 mg	25 mg orally once daily	500 mg intramuscularly day 1, 29 and then every 28 days**
2	3 mg		
3	4 mg		
4	6 mg		
5	9 mg		
6	12 mg		

* Dose Levels may be modified based on emerging safety and PK results.
** Subjects initiating fulvestrant on this study should receive a single additional dose of fulvestrant on Cycle 1 Day 15.

Group 2A and Group 2B will dose escalate independent of each other. In both Groups 2A and Group 2B, each cohort will consist of 3 newly enrolled subjects who will be treated at the specified dose level. After all subjects in each cohort have been followed for at least 28 days after the first dose of GS-5829, a dose-DLT model (Bayesian logistic regression model) utilizing all available GS-5829 safety data will be built, and will provide estimates of DLT rates at all dose levels.

The dose-DLT model recommended dose for the next cohort will be the one having 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%.

Group 3 Lymphoma expansion:

In addition to the minimum 6 subjects in Group 1 with solid tumors or lymphomas who will be enrolled to confirm the MTD, an additional minimum of 6 subjects with aggressive NHL (DLBCL, or PTCL) may be enrolled at a dose no higher than the MTD and complete a 28 day safety period. If ≤ 1 of these 6 subjects reports a DLT within this 28 day safety period, then up to an additional 34 subjects may be enrolled to evaluate the efficacy and tolerability of GS-5829 in lymphoma (a maximum total of 40 subjects with lymphoma enrolled). A minimum of 20 DLBCL and 5 PTCL subjects will be enrolled into this group. If ≥ 2 of 6 subjects report a DLT, then an additional 6 subjects will be enrolled at a lower dose level, or at an alternative dosing schedule, which decreases the total amount of GS-5829 administered over a 28-day period to at least 25% less than the previous cohort (eg 14 days on and 7 days off).

The final dose escalation decisions will be made by the SRT, following a review of the model recommendation and all relevant data available including safety information, PK, biomarkers, clinical data from evaluable patients.

Group 3: Single agent expansion in aggressive lymphomas

Dose Level	GS-5829*	# of subjects enrolled initially	Total number of subjects
1	≤ MTD determined by Group 1	6 subjects	If no DLT in first 6 subjects expand to maximum total of 40 (approx 34 additional subjects)
-1	is ≥25% less total GS-5829 administered over a 28 day period	6 subjects	If no DLT in 6 subjects at this dose level, then expand to maximum total of all Group 3 subjects of 40 (approx 28 additional subjects)

Sites in France will be limited to Group 3 enrollment only.

Dose escalation in Group 1 will continue until identification of the MTD, or a suitable lower recommended dose, for Phase II studies. At least 6 subjects should be treated and evaluated at the GS-5829 dose level recommended for Phase II studies.

A DLT in Group 1 or 2 is a toxicity defined below considered possibly related to GS-5829 occurring during the DLT assessment window (Study Day 1 through C1D28) in each 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 ≥ 3 thrombocytopenia
- 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 medical monitor, may take place to determine if this adverse event (AE) should be assessed as a DLT necessitating dose reduction. However, any Grade 3 or Grade 4 elevation in AST or ALT associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug will be considered a DLT.

	Group 3: For the first 6 subjects enrolled in the aggressive lymphoma group (Group 3), a modification of the DLT assessment for hematologic toxicity will be: • Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3) which persist for > 3 days upon interruption of GS-5829 (administration of growth factors not allowed concurrently, but allowed during GS-5829 interruption) • Grade ≥ 4 thrombocytopenia (< 25,000/mm^3) • Grade ≥ 3 thrombocytopenia (< 50,000/mm^3 to 25,000/mm^3 which persists for > 7 days upon interruption of GS-5829
Number of Subjects Planned:	Up to 160 subjects will be enrolled
Target Population:	Adult subjects with a histologically or cytologically confirmed advanced malignant solid tumor or lymphoma that is refractory to or intolerant of standard therapy or for which no standard therapy is available (Group 1) and post-menopausal women with advanced stage estrogen receptor positive breast cancer who are candidates for exemestane or fulvestrant (Group 2A and Group 2B). The Group 3 lymphoma expansion is limited to DLBCL or PTCL.
Duration of Treatment:	Treatment will continue in the absence of disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.
Diagnosis and Main Eligibility Criteria:	Inclusion Criteria: Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1) Male or female ≥18 years of age. Subjects in Group 2 must be female. 2) Group 1: Histologically or cytologically confirmed advanced malignant solid tumor or lymphoma (any subtype) that is refractory to or intolerant of standard therapy or for which no standard therapy is available.

3) Group 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. Prior chemotherapy for advanced/metastatic disease is allowed.

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

    b. 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)

    c. Post, pre or peri-menopausal subjects considered to be in the post-menopausal state as defined by one of the following:

        i. Age ≥ 60 years

        ii. 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 FSH level within the post menopausal range

        iii. Prior bilateral oophorectomy

        iv. Pre/perimenopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug. If patients have received an alternative LHRH agonist prior to study entry they must switch to goserelin for the duration of the study.

4) Group 3 lymphoma expansion: Subjects with lymphoma are limited to diffuse large B-cell lymphoma or peripheral T-cell lymphoma that are refractory to or intolerant of standard therapy or for which no standard therapy is available.

5) 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])

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

7) Life expectancy of ≥ 3 months, in the opinion of the Investigator
8) 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 growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit). Patients in the Group 3 lymphoma expansion may be enrolled with an ANC of ≥ 1.0 x 10^9/L; Platelets ≥ 75 x 10^9/L.
    b. Hepatic: Aspartate transaminase (AST) / Alanine transaminase (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
9) Coagulation: International Normalized Ratio (INR) ≤ 1.2
10) Negative serum pregnancy test for female subjects (Appendix 7)
11) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol-specified method(s) of contraception as described in Appendix 7.
12) Females who are nursing must agree to discontinue nursing before the first dose of GS-5829
13) 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 Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion
2) Pregnant
3) Known brain metastasis or leptomeningeal disease

4) 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
5) 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 study Day 1
6) Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (ie, larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy) within 28 days of the first dose of study drug
7) 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
8) 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)
9) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives, whichever is longer, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{1/2}$ > 10 days); concurrent use of hormone therapy for prostate cancer is permitted , and concurrent use of exemestane or fulvestrant (and goserelin for pre/perimenopausal breast cancer as per inclusion criteria 2.c.iv) for subjects enrolled in Group 2 (advanced breast cancer) is permitted.
10) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 450 ms for males and > 470 ms for females). Subjects who screen fail due to this criterion are not eligible to be re-screened
11) Prior exposure to bromodomain (BET) inhibitors
12) Clinically significant bleeding within 28 days of study Day 1
13) Known human immunodeficiency virus (HIV) infection

14) HBsAg positive

15) HCV antibody positive

16) 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

17) Evidence of bleeding diathesis

18) History of hemoptysis of ≥ 2.5 mL/1 teaspoon within 6 months of study Day 1

19) History of high grade esophageal or gastric varices

20) No anticoagulation therapy within 7 days of study Day 1, including acetylsalicylic acid, low molecular weight heparin, or warfarin.

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 Study Day 1/C1D1. Screening procedures will include the following: medical history review, physical exam, vital signs, 12-lead electrocardiogram (ECG), ECOG Performance Status, prior/concomitant medication review, blood collection for pregnancy test (females of child bearing potential), chemistry and hematology and coagulation (chemistry, hematology and coagulation to be collected within 7 days of Study Day 1/C1D1), AE assessment, and computed tomography (CT) or magnetic resonance imaging (MRI) (scans that meet protocol requirements that are obtained as part of standard medical practice up to 28 days prior to Study Day 1/C1D1 are acceptable). Subjects who are enrolled in Group 2 will also undergo a baseline radionuclide bone scan. Subjects who are enrolled in Group 3 will undergo a baseline PET/CT in the place of a CT scan if available. Baseline tumor lesions will be measured and characterized prior to Study Day 1/C1D1 to assess the subject disease status prior to beginning treatment.

Treatment:

Subjects who meet eligibility criteria will receive GS-5829 orally once daily. Subjects in the first 3 cohorts of Group 1 will receive a single dose of GS-5829 and then approximately 7 days later start their first 28 day cycle of GS-5829 once daily. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including 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), urine pregnancy test (every 4 weeks while receiving GS-5829 in female of childbearing potential), and assessment of AEs. In addition, subjects will undergo CT/MRI or applicable scans every 8 weeks for the first year and then every 12 weeks. Subjects in Group 3 will undergo a PET/CT if available instead of a CT scan alone at week 16. A subject who does not show evidence of disease progression by clinical assessment or by CT/MRI or applicable scan may continue receiving GS-5829 once daily until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.5.

Plasma samples for GS-5829 PK will be collected (± 10 minutes) in cohorts 1-3 of Group 1 on Study Day 1 at pre-dose (0hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose and in cohorts 4-8 of Group 1 and all cohorts of Group 2 on Cycle 1 Day 1 at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Additional samples will be collected at 48 and 72 hours post-dose in cohorts 1 – 3 of Group 1 relative to first dose of GS-5829. Plasma samples for GS-5829 PK will be collected in all cohorts (Group 1 and Group 2) at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose relative to GS-5829 administration on Cycle 1 Day 8. Sparse PK samples will be collected in all cohorts (Group 1 and Group 2) at trough (20-26 hours post-dose) on Cycle 1 Day 4, 2 - 4 hours post-dose on Cycle 1 Day 15, and anytime post-dose on Day 1 of Cycles 2 through 6. In one or more cohorts, PK samples will be collected on Day 1 of Cycle 2 at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose. GS-5829 dose will be administered in fed state on Day 1 of Cycle 2.

Urine will be collected for GS-5829 PK in Group 1 cohorts 1-3 on Study Day 1 and in Group 1 cohorts 4-8 on Cycle 1 Day 1 at pre-dose, 0-6 hours, 6-12 hours, and 12-24 hours post-dose relative to first dose of GS-5829.

Subjects in the Group 3 lymphoma expansion will have PK drawn at pre-dose, 1, 2, 4, 6, and 24 hours post-dose on Cycle 1, Day 8. PK samples will also be drawn at pre-dose on Day 1 of Cycles 2, 4, and 6.

After discontinuation of treatment, subjects will be followed for safety for 30 days.

Test Product, Dose, and Mode of Administration:	GS-5829 tablets will be self-administered orally once daily, beginning on Cycle 1 Day 1 of the study and thereafter at approximately the same time each day until end of treatment. Subjects in the first 3 Dose Levels will be administered GS-5829 in the clinic as a single dose and then 7 days later will self-administer GS-5829 orally once daily. GS-5829 is supplied as 0.2, 1, 5, and 10 mg tablets. For subjects in Group 2A, exemestane tablets will be self-administered orally once daily, beginning on Cycle 1 Day 1 of the study and thereafter at approximately the same time each day until the end of treatment. For subjects in Group 2B, fulvestrant will be administered intramuscularly by the clinic staff on Cycle 1 Day 1, Cycle 1 Day 15 and Cycle 2 Day 1 of the study and thereafter at approximately every 28 days (+/- 3 days) until the end of treatment.
Reference Therapy, Dose, and Mode of Administration:	Not Applicable
Criteria for Evaluation:	
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	Efficacy will be evaluated by overall response rate (ORR) (complete response [CR] + partial response [PR], assessed as per RECIST v1.1 or appropriate evaluation such as Cheson Criteria for lymphoma or based on the Prostate Cancer Working Group [PCWG] for prostate cancer) and progression-free survival (PFS), defined as the interval from first dose date of study drug to the earlier of the first documentation of definitive disease progression or death from any cause.
Pharmacokinetics:	The following PK parameters for GS-5829 will be calculated as applicable: C_{max}, AUC_{last}, AUC_{tau}, C_{tau}, T_{max}, and $t_{1/2}$

Statistical Methods:

Analysis Methods

The Full Analysis Set (FAS) will be used in the analyses of subject characteristics and efficacy endpoints. The FAS consists of all subjects who receive ≥ 1 dose of study drug. A Safety Analysis Set for this study will be the same as FAS since this study is a non-randomized study. Other analysis sets (DLT-Evaluable and PK/PD analysis sets) will be used for additional analyses as well.

Subject characteristics and study results will be described and summarized by group (Group 1, Group 2A and Group 2B, Group 3 lymphoma expansion), dose level, and assessment 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.

Efficacy endpoints, ORR and PFS, will be listed only.

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 PK and PD Analysis Sets, GS-5829 plasma concentrations and PK parameters and whole blood PD markers will also be described and summarized. Plasma concentrations of GS-5829 metabolite(s) may also be determined and PK explored.

Sample Size

The sample size of the study will be determined based on the number of dose levels evaluated and the emerging GS-5829-related toxicities. The study will consist of up to 160 subjects.

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

AAG	Alpha-1 Acid Glycoprotein
ABC	activated B-cell
AE	adverse event
AI	aromatase inhibitor
ALT	alanine transaminase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APTT	Activated partial thromboplastin time
AR	androgen receptor
AR-V7	AR splice variant 7
AST	aspartate transaminase
AUC	area under the concentration versus time curve
BCL	B-cell lymphoma
BCRP	breast cancer resistance protein
BET	bromodomain and extra-terminal
BRD	bromodomain
CA 15-3	cancer antigen 15-3
CA 19-9	carbohydrate antigen 19-9
CA 27.29	cancer antigen 27.29
CA-125	cancer antigen-125
CDK 4/6	cyclin-dependent kinase 4/6
CEA	carcinoembryonic antigen
CP17	centromeric probe for chromosome 17
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
CTC	circulating tumor cells
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

E2	estradiol
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
ER	estrogen receptor
eSAE	electronic SAE
FAS	full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
Hb	hemoglobin
HBsAg	Hepatitis B surface Antigen
hCG	human chorionic gonadotropin
HCV	hepatitis c virus
HED	human equivalent dose
HER2	human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HNSTD	highest non-severely toxic dose
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IP	investigational product
IRB	Institutional Review Board
IUD	intrauterine device
IxRS	Interactive voice/web Response System
LD	longest diameter
LHRH	lutenizing hormone-releasing hormone
LPD	longest perpendicular diameter
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
ORR	overall response rate
PCWG	Prostate Cancer Working Group
PD	pharmacodynamics
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response

PSA	prostate-specific antigen
PT	prothrombin time
PTCL	peripheral T cell lymphoma
QD	every day
QTc	corrected QT interval
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
RDP2	Recommended dose for phasae 2
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RNAPII	RNA polymerase II
SADR	serious adverse drug reaction
SAE	serious adverse event
SOC	system organ class
SOP	standard operating procedure
SPD	sum of the product
SRT	safety review team
STD	severely toxic dose
StD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
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 2014a}. 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.

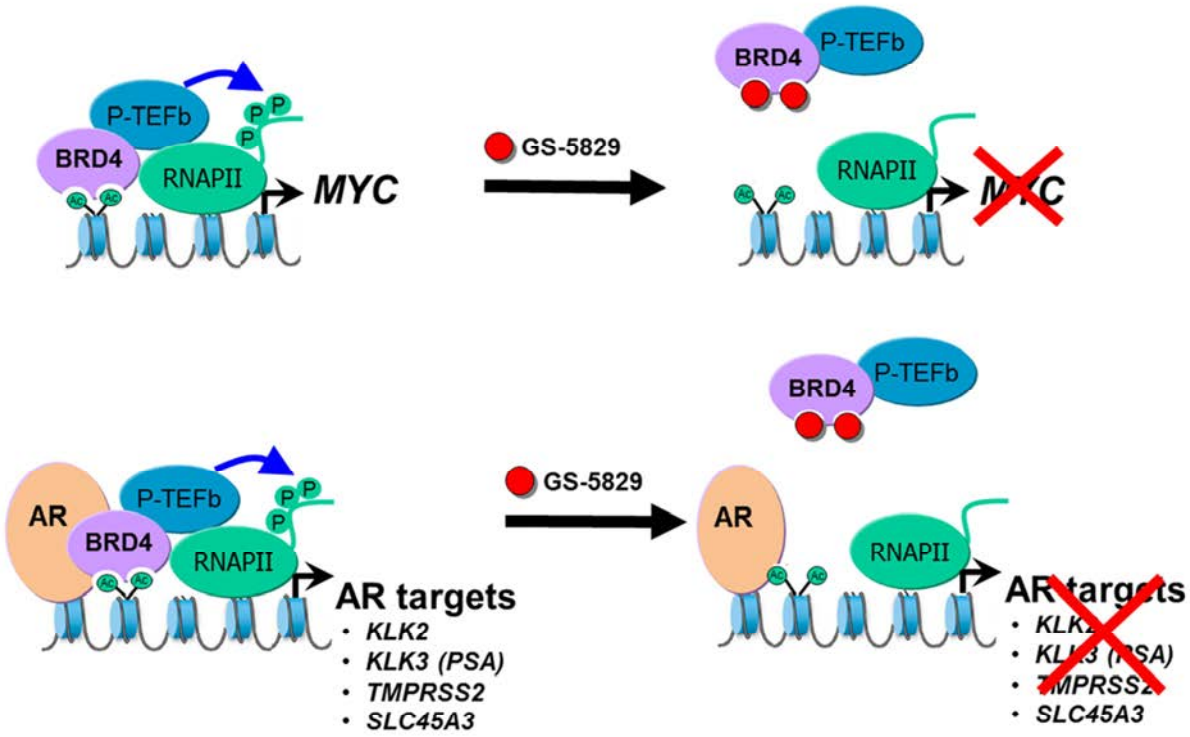
BRD2, 3, 4 are essential regulators of the expression or activity of several key oncogenic transcription factors, including v-myc avian myelocytomatosis viral oncogene homolog (MYC) and the androgen receptor (AR) {Shi et al 2014a}. Transcription of the MYC gene is dependent on BET proteins in many cells {Mertz et al 2011} (Figure 1-1). 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 patients 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), estrogen receptor positive advanced stage breast cancer 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 and the ER in breast cancer cells.

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



Bromodomain and extraterminal proteins, including BRD4, are recruited to the MYC promoter and enhancer elements through an interaction between the tandem bromodomains and acetylated histone proteins in chromatin (top panel). BRD4 recruits the positive transcription elongation factor b (pTEFb) complex to the MYC gene, which phosphorylates RNAPII to increase transcription of the MYC gene. GS-5829 binds to the bromodomains of BET proteins, thereby blocking the interaction with acetylated histone proteins and leading to a reduction of MYC transcription. GS-5829 similarly functions to inhibit the transcription of AR target genes in prostate cancer cells, including the kallikrein-related peptidase 3 (KLK3) gene that encodes prostate specific antigen (bottom panel).

1.2. GS-5829

1.2.1. General Information

For further information on 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 clear 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, shows high forward permeability across Caco-2 monolayers, and low efflux, but GS-5829 is a substrate of human P-g and 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 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. The dog was the more sensitive species, with the no-observed-adverse-effect levels in the mouse and dog 10 and 0.03 mg/kg/day respectively. The severely toxic dose in 10% of mice and the highest HNSTD in dogs were 25 and 0.1 mg/kg/day, respectively.

Hematopoietic effects include decreases in white blood cells, 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 the 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 the 0.3 mg/kg/day in 1 of 6 dogs. The mechanism for the hemorrhage is not known. Protime and partial thromboplastin time measurements were normal. The anatomic pattern of the hemorrhage in the lung field and microscopy appears were 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 mg 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

Study GS-US-350-1604, a Phase 1b/2 study to evaluate the safety, tolerability, PK and pharmacodynamics of GS-5829 as a single agent and in combination with enzalutamide in subjects with CRPC, initiated in November 2015 and is actively enrolling.

1.2.4. Information on 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 postmenoapusal 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 prescribing information (Appendix 9) or the summary of product characteristics in the pharmacy binder.

1.2.5. Information on 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 downregulates 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 antiestrogen therapy. For current information about fulvestrant (Faslodex®), refer to the prescribing information (Appendix 10) or the summary of product characteristics in the pharmacy binder

1.3. Rationale for Development of GS-5829 in Advanced Solid Tumors and Lymphomas (Group 1)

In 2014, it is estimated that over 500,000 people will die from cancer in the United States (US) alone, with the vast majority due to progression of advanced stage solid tumors {National Cancer Institute 2014}. Strong evidence exists that the *MYC* oncogene family plays a critical role in the pathogenesis of many of these cancers. Overexpression or amplification of *MYC* has been observed in prostate, breast, colorectal, gastric, melanoma, non-small cell lung, small cell lung, medullary thyroid cancer, rhabdomyosarcoma, multiple myeloma, and aggressive non-Hodgkin's lymphomas such as Burkett's and DLBCL {He et al 2014, Koh et al 2010, Lin et al 2010, Molyneux et al 2012, Nair et al 2014, Nesbit et al 1999, Odia et al 2013, Petrich et al 2014, van Dam et al 1994, Yoo et al 2004}. GS-5829 is expected to have broad activity in tumors that overexpress MYC by decreasing the transcription of MYC RNA. GS-5829 also has potential for activity in tumor types that are highly dependent on the activity of other oncogenic transcription factors regulated by BET proteins. These include the AR in prostate cancer {Asangani et al 2014}, the estrogen receptor and Twist in breast cancer {Feng et al 2014, Shi et al 2014b}, FOS-like antigen 1 in nonsmall cell lung cancer and pancreatic cancer {Lockwood et al 2012, Sahai et al 2014}, and Smoothened in basal cell carcinoma and medulloblastoma {Tang et al 2014}.

In 2014, it is estimated that there will be 233,000 new cases of prostate cancer and 29,480 deaths due to prostate cancer in the US {National Cancer Institute 2014}. The majority of men (approximately 90%) are diagnosed with loco-regional disease that is treated surgically and/or with radiation therapy; 5-year survival approaches 100% for these patients. However, despite the availability of a variety of therapies, including pharmacological inhibitors of AR activity, immunotherapy, radiation, and chemotherapy, metastatic prostate cancer has a 5-year survival of only 30%, with most patients dying from prostate cancer.

In patients with advanced prostate cancer who have progressed while receiving therapy with chemical or surgical castration, the androgen/AR axis remains the target of current standard of care agents abiraterone and enzalutamide. Primary and acquired resistance to such agents occurs when the AR is activated in an androgen-independent manner, most notably through the expression of the constitutively active AR splice variant 7 (AR-V7) {Antonarakis et al 2014, Guo et al 2009}. In nonclinical studies, GS-5829 inhibited growth and induced apoptosis in

prostate cancer cell lines by inhibiting MYC expression and AR-target gene expression in both AR- and AR-V7-expressing prostate cancer cell lines.

Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin's lymphoma, accounting for approximately 30% of all lymphoma diagnoses {Morton et al 2006}. Currently, the combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is considered to be the standard of care for DLBCL. While approximately half of patients with DLBCL achieve durable remissions, patients who relapse or who are refractory to primary therapy have a poorer outcome. For patients who are not transplant eligible, salvage therapies, which generally include chemotherapy with or without rituximab, offer little chance of prolonged disease control. Response rates range from 30% to 60%, with overall survival less than 12 months {Vacirca et al 2014}.

GS-5829 is being developed for the treatment of DLBCL based on the known role of BET proteins to regulate the transcription of key oncogenic pathways related to MYC, B-cell lymphoma 6 (BCL6), and nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) {Ceribelli et al 2014, Chapuy et al 2013}. In nonclinical studies, GS-5829 reduces the transcription of MYC in DLBCL cell lines vitro and in vivo, resulting in potent cell growth inhibition and/or apoptosis. GS-5829 exhibits equivalent potent activity in DLBCL cell lines irrespective of known poor prognosis factors for patients, including activated B-cell (ABC) subclass or MYC/B-cell lymphoma 2 (BCL2) coexpression.

1.3.1. Rationale for Development of GS-5829 in Combination with Exemestane or Fulvestrant for the Treatment of Estrogen Receptor Positive Breast Cancer (Group 2)

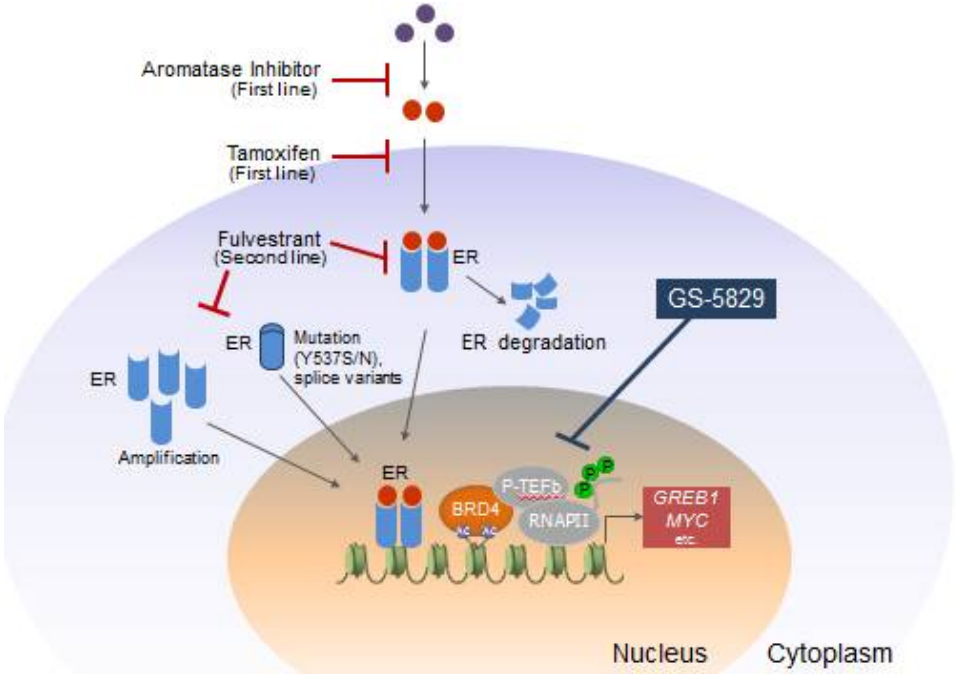
Approximately 75% of breast cancers express the estrogen receptor (ER), a nuclear hormone receptor and transcription factor that promotes the expression of genes involved in cell growth and survival {Clark et al 1984}. Anti-estrogen endocrine therapies, such as aromatase inhibitors (AIs) and tamoxifen 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 anti-estrogen therapy significantly improves progression-free survival (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}.

We hypothesize that 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 (Figure 1-2). 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 cell breast cancer lines in vitro and to inhibit growth of patient-derived ER-positive breast cancer xenografts in mice.

Figure 1-2. 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.

1.3.2. Rationale to Evaluate GS-5829 in Specific Aggressive Non-Hodgkin's Lymphoma: DLBCL and PTCL (Group 3)

Specific subtypes of aggressive lymphoma may have a greater potential for sensitivity to BETi. DLBCL and PTCL are included in this category and are also notable for poor OS for patients in the relapsed and/or refractory setting who are not bone marrow transplant candidates; 9-12 months for relapsed DLBCL {Nagle et al 2013} and 5.5 months for PTCL {Mak et al 2013}. These dismal OS rates highlight an urgent need for improved therapeutic options.

In mature T-cell lymphomas, such as PTCL, BET inhibition may be a favorable target. Cell cycle arrest and reduction of MYC mRNA levels in five out of seven anaplastic large-cell T-cell lymphoma cell lines has been reported with the BETi, OTX-015 {Bonetti et al 2012}.

Data supporting the single agent evaluation of BETi in treating DLBCL have been discussed in Section 1.3.1.

1.3.3. Rationale for the Dose Selection

The starting dose of 0.6 mg GS-5829 was selected based on preclinical repeat-dose toxicology data, where this dose represented 1/6 the highest non-severely toxic dose (HNSTD) in dog, the most sensitive nonclinical species tested. This dose is commensurate with the recommendation outlined in the ICH Guidance for Industry, "S9 Nonclinical Evaluation for Anticancer Pharmaceuticals" (March 2010). The starting dose of 0.6 mg GS-5829 once daily provided margins of approximately 203-fold of the severely toxic dose (STD10) in the mouse (25 mg/kg/day) and 5.5-fold of the HNSTD in the dog (0.1 mg/kg/day) on a human equivalent dose (HED) basis as determined in the repeat dose toxicity studies.

PK data from the first 3 dose levels suggests that exposure in humans is higher than initially predicted and therefore additional intermediate dose levels have been added.

Based on preliminary pharmacokinetic data in the early dose levels of this study, the potentially clinically efficacious exposure (AUC 2.5 h.µg/mL) in humans is anticipated to be achieved with once daily dosing of 3 to 4 mg of GS-5829, which is anticipated to achieve adequate target inhibition for a portion of the dosing interval as supported by in vivo preclinical data.

Dose Levels of 0.6, 1.4, 2.0 and 3.0 enrolled a single subject with the plan to expand to at least 3 subjects if a ≥ Grade 2 treatment-related toxicity was observed within the initial dosing period (Study Day 1 through C1D28). No drug related toxicities were observed at Dose Levels 0.6 through 2.0 mg. Should a ≥ Grade 2 treatment-related toxicity be observed in the subject receiving 3.0 mg, then a standard 3+3 study design will initiate at the 3.0 mg dose. Should no ≥ Grade 2 treatment-related toxicity be observed in the subject receiving 3.0 mg dose, the next dose to be enrolled, Dose Level 4.0 mg will expand enrollment to at least 3 subjects and the study will proceed with a standard 3 + 3 study design. The study will proceed until MTD is identified.

Due to the narrow therapeutic index observed in dogs, the percentage dose increment sequentially decreases at each dose level.

The breast cancer arm of the study (Group 2A and 2B) will initiate at 2.0 mg which has been demonstrated to be safe and tolerable in patients with advanced stage solid tumors and lymphoma in Group 1 of this study. No drug interactions or overlapping toxicities are expected between GS-5829 and exemestane or fulvestrant. Group 2 will not dose escalate beyond the single agent MTD of GS-5829.

The Group 3 lymphoma expansion arm will initiate at a dose ≤ to the MTD as determined in Group 1; e.g. a dose that has been demonstrated to be safe and tolerable in patients with advanced stage solid tumors and lymphoma in Group 1 of this study.

1.4. Compliance

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

1.5. 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 sign of toxicity in human studies, a toxicity which may be easily monitored.

Target organs identified in the repeat-dose toxicity studies included hematopoietic and male reproductive systems (mice and dogs), the adrenal glands (mice), and the GI tract and respiratory system (dogs). With the exception of the adrenal glands in the mouse and the respiratory system in dogs, all other target organs are expected based on the known pharmacology of GS-5829 to inhibit BET proteins. The effects on the hematopoietic system, male reproductive tract, adrenal glands, and GI tract were considered reversible and can be monitored in the clinic.

As of a data cutoff of 12 October 2015, in this First-In-Human study GS-US-350-1599 no deaths resulting from adverse events (AEs) have occurred. Two subjects experienced 3 serious adverse events (SAEs) which were considered by the investigator to be Grade 3 and not related to study drug (cholangitis and sepsis in 1 subject at 0.6 mg and thrombocytopenia in 1 subject at 1.4 mg). The following AEs were considered related to study drug: fatigue (1 subject, 0.6-mg group and 1 subject, 1.4-mg group), nausea (1 subject, 0.6-mg group and 1 subject, 1.4-mg group), splenomegaly (1 subject, 1.4-mg group), and dizziness (1 subject, 1.4-mg group). No AEs lead to discontinuation of study drug. After the data cut, a DLT of adrenal hemorrhage was reported in a subject receiving 4 mg of GS-5829. The subject had normal coagulation parameters and a platelet count higher than normal at baseline which did not change at the time of the event. An additional DLT of Grade 3 thrombocytopenia was reported in a subject receiving 3 mg of GS-5829.

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 followed by a 30-day Safety Follow-Up Visit. Physical examinations will occur on Day 1of each 28-day cycle until end of treatment, 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.

Potential Benefits

The primary potential benefit of BET inhibition is that therapy may delay progression or improve overall survival in patients with lymphoma or solid tumor who do not have alternative therapies which have been demonstrated to provide significant clinical benefit. For patients with breast cancer, the potential benefit of BET inhibition administered in combination with standard anti-estrogen therapy is to delay progression or improve overall survival.

Participants are informed that their involvement in the study may offer benefits to other current or future cancer patients by enhancing knowledge relating to treatment.

2. OBJECTIVES

The primary objectives of this study are:

- Characterize the safety and tolerability of GS-5829 as a monotherapy in subjects with advanced solid tumors and lymphomas
- Determine the MTD or recommended dose for phase 2 study (RDP2) of GS-5829 as a monotherapy in subjects with advanced solid tumors and lymphomas
- Characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer
- Determine the MTD or RDP2 of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer

The secondary objective of this study is:

- Evaluate the PK of GS-5829 alone in subjects with advanced solid tumors and lymphomas and in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer

CCI [redacted]

3. STUDY DESIGN

3.1. Endpoints

The endpoints for this study are described in Section 8.

3.2. Study Design

This is an open-label, multicenter, sequential dose-escalation study to evaluate the safety, tolerability, PK, and PD of GS-5829 as a single agent in subjects with advanced solid tumors and lymphomas and in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer.

Group 1: **Single agent GS-5829 in solid tumors and lymphomas**

Cohorts of subjects with advanced solid tumors and lymphomas who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive oral GS-5829 as monotherapy once daily (QD). The starting dose will be 0.6 mg. Each dose level will enroll 1 subject until a ≥ Grade 2 treatment-related toxicity is observed within the initial dosing period (Study Day 1 through C1D28 for all cohorts). At Dose Level 5 or if a ≥ Grade 2 treatment-related toxicity is observed (whichever occurs first), the dose level will be expanded to 3 subjects. (Note: subjects enrolled with a Grade 2 hemoglobin [Hb] must have Hb worsen by at least 1 grade from baseline to be considered for expansion of the cohort to 3 subjects). Once a dosing level has been expanded to 3 subjects, a standard 3+3 study design will begin and, dose escalation [3+3] will be performed with cohort sizes of 3 to 6 subjects. Subjects in the first 3 cohorts will receive a single dose and then approximately 7 days later, initiate dosing once daily. Subjects will return to the clinic for frequent evaluation and monitoring as per Appendix 2.

The doses for each candidate dose level in Group 1 are shown in Table 3-1.

Table 3-1. Group 1: Single Agent GS-5829

Dose Level	GS-5829*
1	0.6 mg
2	1.4 mg
3	2 mg
4	3 mg
5	4 mg
6	6 mg
7	9 mg
8	12 mg

* Dose levels may be modified based on emerging safety and PK results.

If a DLT occurs within the 28 day DLT period at any dose level, this level will be expanded to enroll 3 additional subjects.

The safety and tolerability of each dose level will be assessed by a safety review team (SRT) after all subjects in the cohort have been followed for at least 28 days after the first dose of GS-5829. If no DLTs occur in up to 3 subjects or < 2 DLTs occur in up to 6 subjects on any Dose Level after 28 days on treatment, the next Dose Level will open. Each subsequent Dose Level will open if the Dose Level preceding has no DLTs in 3 subjects or < 2 DLTs in up to 6 subjects.

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

Prior to initiating enrollment for Dose Level 4 in Group 1, an analysis of all available safety, PK, and PD data from previous cohorts will be reviewed.

If a subject is enrolled in a dose level but does not complete the PK or PD analysis, they may continue on study but an additional subject may be enrolled at that dose level.

The MTD is the highest dose level with a subject incidence of ≤ 1 DLT during the first 28 days of study drug dosing of 6 subjects. A minimum of 6 subjects need to be treated at a dose level before this dose level can be deemed as the MTD.

Group 2: **Combination therapy of GS-5829 with exemestane or fulvestrant in patients with advanced stage estrogen receptor positive breast cancer**

Cohorts of subjects with advanced estrogen receptor positive breast cancer 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 full standard doses of exemestane or fulvestrant. The starting dose of GS-5829 will be 2.0 mg QD, which is a dose level that has been demonstrated to be safe and tolerable (no Grade 2 or higher drug related toxicity) in patients with solid tumors and prostate cancer. Dose escalation will continue with cohort sizes of 3-6 subjects in parallel arms: Group 2A will initiate with 2.0 mg of GS-5829 orally once daily on Cycle 1 Day 1 combined with 25 mg of exemestane once daily beginning on Cycle 1 Day 1. The subject may initiate exemestane anytime prior to, or on, Cycle 1 Day 1. Group 2B will initiate with 2.0 mg of GS-5829 orally once daily on Cycle 1 Day 1 with 500 mg fulvestrant administered intramuscularly (Cycle 1 Day 1 and then every 28 days (+/- 3 days). If Cycle 1 Day 1 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 for each candidate dose level in group 2 are shown in Table 3-2.

Table 3-2. Group 2: Combination of GS-5829 in Breast Cancer

Dose Level	GS-5829*	Group 2A Exemestane	Group 2B Fulvestrant
1	2 mg	25 mg orally once daily	500 mg intramuscularly day 1, 29 and then every 28 days**
2	3 mg		
3	4 mg		
4	6 mg		
5	9 mg		
6	12 mg		

* Dose Levels may be modified based on emerging safety and PK results.
** Subjects initiating fulvestrant on this study should receive a single additional dose of fulvestrant on Cycle 1 Day 15.

Group 2A and Group 2B will dose escalate independent of each other. In both Group 2A and Group 2B, each cohort will consist of 3 newly enrolled subjects who will be treated at the specified dose level. After all subjects in each cohort have been followed for at least 28 days after the first dose of GS-5829, a dose-DLT model (Bayesian logistic regression model) utilizing all available GS-5829 safety data will be built and will provide estimates of DLT rates at all dose levels. The dose-DLT model recommended dose for the next cohort will be the one having the highest chance that the DLT rate will fall in the target interval [16%, 33%) and a probability of <25% that the DLT rate exceeds 33%.

Group 3 Lymphoma expansion:

In addition to the minimum 6 subjects in Group 1 with solid tumors or lymphomas who will be enrolled to confirm the MTD, an additional minimum of 6 subjects with aggressive NHL (DLBCL or PTCL) may be enrolled at a dose no higher than the MTD and complete a 28 day safety period. If ≤ 1 of these 6 subjects reports a DLT within this 28 day safety period, then up to an additional 34 subjects may be enrolled to evaluate the efficacy and tolerability of GS-5829 in lymphoma (a maximum total of 40 subjects with lymphoma enrolled). A minimum of 20 DLBCL and 5 PTCL subjects will be enrolled into this group. If ≥ 2 of 6 subjects report a DLT, then an additional 6 subjects will be enrolled at a lower dose level, or at an alternative dosing schedule, which decreases the total amount of GS-5829 administered over a 28-day period to at least 25% less than the previous cohort (eg 14 days on and 7 days off).

The final dose escalation decisions will be made by the SRT, following a review of the model recommendation and all relevant data available including safety information, PK, CCI [redacted] clinical data from evaluable patients.

Table 3-3. Group 3: Single agent expansion in aggressive lymphomas

Dose Level	GS-5829*	# of subjects enrolled initially	Total number of subjects
1	≤ MTD determined by Group 1	6 subjects	If no DLT in first 6 subjects expand to maximum total of 40 (approx. 34 additional subjects)
-1	is ≥25% less total GS-5829 administered over a 28 day period	6 subjects	If no DLT in 6 subjects at this dose level, then expand to maximum total of all Group 3 subjects of 40 (approx. 28 additional subjects)

Sites in France will be limited to Group 3 enrollment only.

Dose escalation in Group 1 will continue until identification of the MTD, or a suitable lower recommended dose, for Phase II studies. At least 6 subjects should be treated and evaluated at the GS-5829 dose level recommended for Phase II studies.

A DLT in Group 1 or 2 is a toxicity defined below considered possibly related to GS-5829 occurring during the DLT assessment window (Study Day 1 through C1D28) in each cohort.

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm3)
- 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 ≥ 3 thrombocytopenia
- 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 Medical Monitor may take place to determine if

this AE should be assessed as a DLT necessitating dose reduction. However, any Grade 3 or Grade 4 elevation in AST or ALT associated with a Grade 2 elevation in bilirubin that is at least possibly related to study drug will be considered a DLT.

Group 3: For the first 6 subjects enrolled in the aggressive lymphoma group (Group 3), a modification of the DLT assessment for hematologic toxicity will be:

- Grade ≥ 4 neutropenia (absolute neutrophil count [ANC] < 500/mm^3) which persist for > 3 days upon interruption of GS-5829 (administration of growth factors not allowed concurrently, but allowed during GS-5829 interruption)
- Grade ≥ 4 thrombocytopenia (< 25,000/mm^3)
- Grade ≥ 3 thrombocytopenia (< 50,000/mm^3 to 25,000/mm^3 which persists for > 7 days upon interruption of GS-5829

3.3. Study Treatments

Subjects who meet eligibility criteria will receive GS-5829 orally once daily. Subjects in the first 3 cohorts will receive a single dose of GS-5829 and then approximately 7 days later start their first 28 day cycle of GS-5829 once daily. Each cycle will consist of 28 days. Safety and efficacy assessments will occur on an outpatient basis including assessment of tumor response, physical exam, vitals, electrocardiogram (ECG), collection of blood samples (for routine safety labs, GS-5829 PK, CCI [redacted] at applicable visits), urine pregnancy (every 4 weeks while receiving GS-5829 in females of childbearing potential), and assessment of AEs. In addition, subjects will undergo computed tomography (CT)/magnetic resonance imaging (MRI) or applicable scans every 8 weeks for the first year and then every 12 weeks. Subjects in Group 3 will undergo a PET/CT if available instead of a CT scan alone at week 16.

A subject who does not show evidence of disease progression by clinical assessment or by CT/MRI or applicable scan may continue receiving GS-5829 once daily day until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Section 3.4.

For subjects in Group 2, a radionuclide bone scan (whole body) is also required at screening and then as clinically indicated or to confirm a complete response.

Study drug dosing will continue in the absence of disease progression or toxicity warranting discontinuation of therapy.

3.4. Criteria for Discontinuation of Study Drug

Study medication may be discontinued in the following instances:

- Documented progression of malignant disease
- Pregnancy

- Investigator discretion
- Non-compliance with study drug
- Subject never dosed with study drug
- Protocol violation
- 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

3.5. Criteria for Removal from Study

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

- Documented progression of malignant disease
- Death
- Pregnancy
- Investigator discretion
- Non-compliance with study drug
- Protocol violation
- Withdrawal of consent
- Lost to follow-up
- Study termination by the sponsor

4. SUBJECT POPULATION

4.1. Number of Subjects and Subject Selection

Up to 160 subjects who meet the eligibility criteria will be enrolled.

4.2. Inclusion Criteria

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

1) Male or female ≥ 18 years of age. Subjects in Group 2 must be female.

2) Group 1: Histologically or cytologically confirmed advanced malignant solid tumor or lymphoma (any subtype) that is refractory to or intolerant of standard therapy or for which no standard therapy is available.

3) Group 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. Prior chemotherapy for advanced/metastatic disease is allowed.

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

    b. 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)

    c. Post, pre or peri-menopausal subjects to be in the post-menopausal state as defined by one of the following:

        i. Age ≥ 60 years

        ii. 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 FSH level within the post-menopausal range

        iii. Prior bilateral oophorectomy

        iv. Pre/perimenopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to first dose of study drug. If patients have received an alternative LHRH agonist prior to study entry they must switch to goserelin for the duration of the study.

4) Group 3 lymphoma expansion: Subjects with lymphoma are limited to diffuse large B-cell lymphoma or peripheral T-cell lymphoma that are refractory to or intolerant of standard therapy or for which no standard therapy is available

5) 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])

6) ECOG Performance Status of ≤ 1

7) Life expectancy of > 3 months, in the opinion of the Investigator

8) 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 growth factors within previous 7 days of the hematologic laboratory values obtained at screening visit). Patients in the Group 3 lymphoma expansion may be enrolled with an ANC of ≥ 1.0 x 10^9/L; Platelets ≥ 75 x 10^9/L.

   b. Hepatic: Aspartate transaminase (AST) / Alanine transaminase (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

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

10) Negative serum pregnancy test for female subjects (Appendix 7)

11) Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in Appendix 7.

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

13) 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 Medical Monitor would pose a risk to subject safety or interfere with the study evaluations, procedures, or completion

2) Pregnant

3) Known brain metastasis or leptomeningeal disease

4) 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

5) 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 study Day 1

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

7) 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

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

9) Anti-tumor therapy (chemotherapy, antibody therapy, molecular targeted therapy) within 21 days or 5 half-lives, whichever is longer, of study drug dosing (6 weeks for nitrosoureas, mitomycin C, or molecular agents with $t_{½}$ > 10 days); concurrent use of hormone therapy for prostate cancer is permitted, and concurrent use of exemestane or fulvestrant (and goserelin for pre/perimenopausal breast cancer as per inclusion criteria 2.c.iv) for subjects enrolled in Group 2 (advanced breast cancer) is permitted

10) History of long QT syndrome or whose corrected QT interval (QTc) measured (Fridericia method) at screening is prolonged (> 450 ms for males and > 470 ms for females). Subjects who screen-fail due to this criterion are not eligible to be re-screened

11) Prior exposure to BET inhibitors

12) Clinically significant bleeding within 28 days of study Day 1

13) Known human immunodeficiency virus (HIV) infection

14) HBsAg positive

15) HCV antibody positive

16) Use of strong/moderate CYP3A4 inhibitors or strong/moderate CYP3A4 inducers within 2 weeks prior to the first dose of study drug

17) Evidence of bleeding diatheses

18) History of hemoptysis of ≥ 2.5 mL/1 teaspoon within 6 months of study Day 1

19) History of high grade esophageal or gastric varices

20) No active anticoagulation within 7 days of study Day 1; including acetylsalicylic acid, low molecular weight heparin, or warfarin.

5. INVESTIGATIONAL MEDICINAL PRODUCTS

5.1. Enrollment

It is the responsibility of the Investigator to ensure that subjects are eligible for the study prior to enrollment. Subjects will be assigned a unique screening number at the time of consent.

Once eligibility is confirmed subjects will be assigned a unique subject number. 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. Once a subject number is assigned to a subject, it will not be reassigned to another subject.

Sites in France will be limited to Group 3 enrollment only.

5.2. Description and Handling of GS-5829, Exemestane and Fulvestrant

5.2.1. Formulation

GS-5829 will be supplied as gray, plain-faced, film-coated, round tablets containing either 0.2, 1, or 10 mg GS-5829 (0.24, 1.22 or 12.20 mg GS-5829-02, phosphate salt form of GS-5829, respectively). Also, GS-5829 will be supplied as orange, plain-faced, film-coated, round tablets containing 5 mg GS-5829 (6.10 mg GS-5829-02, phosphate salt form of GS-5829). In addition to the active ingredient, 0.2 mg, 1 mg, and 10 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 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.

Exemestane and fulvestrant are commercially sourced. Information regarding the formulation can be found in the current prescribing information.

5.2.2. Packaging and Labeling

GS-5829 tablets (0.2, 1, 5, and 10 mg) are packaged 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.

GS-5829 bottles 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.

Sufficient quantities of GS-5829 tablets will be shipped to the investigator or qualified designee from Gilead Sciences Clinical Supplies Management (or its designee).

Exemestane and fulvestrant will 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. The study center will be required to maintain a log of daily temperature readings in the storage area for the duration of the study. To ensure the stability and proper identification, the drug product should not be stored in a container other than the container in which they were 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 through inhalation when handling GS-5829 tablets.

Exemestane and fulvestrant are commercially sourced. Information regarding the storage condition can be found in the current prescribing information.

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. The first 3 cohorts of subjects will take a single dose of GS-5829 and then approximately 7 days later take their dose of study drug at approximately 24-hour intervals. Subjects in dose levels 4-8 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.

At one or more dose levels, GS-5829 dose will be administered in fed state with a standardized meal (~500 to 600 calories and ~30% of calories from fat) on Day 1 of Cycle 2.

If the subject misses a dose, he/she should be instructed to take the study drug as soon as he/she remembers, unless more than 8 hours has elapsed since the scheduled time of the missed dose. In this case, the subject should be instructed to wait and take the next dose at the regularly scheduled time. Subjects should not take more than 1 dose of study drug at a time.

If a subject vomits within 5 minutes of dosing and the tablet is visible, the subject should be instructed to re-dose. If a subject vomits more than 5 minutes after dosing or if the tablet is not visible, the subject should be instructed to wait and take the next dose at the regularly scheduled time.

Aromasin® (exemestane) will be supplied as 25 mg tablets for oral administration. Subjects assigned to receive exemestane in combination with GS-5829 in the study will self-administer exemestane orally once daily, beginning on or before Cycle 1 Day 1 of the study and thereafter at approximately the same time each day until the end of treatment. Refer to Appendix 9 for further details.

Faslodex® (fulvestrant) is supplied as 50 mg/mL for intramuscular administration. Subjects assigned to receive fulvestrant in combination with GS-5829 in this study will receive fulvestrant on Cycle 1 Day 1 and every 28 days (+/- 3 days) until the end of treatment. For subjects initiating fulvestrant on this study, a single additional dose of fulvestrant 500 mg should be administered on Cycle 1 Day 15 (+/- 3 days). Fulvestrant should be administered intramuscularly into the buttocks slowly (1 – 2 minutes per injection) as two 5mL injections, one in each buttock. Refer to Appendix 10 for further details.

5.4. Prior and Concomitant Medications

In vitro data indicate 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 administration. Examples of moderate and strong CYP3A4 inhibitors and inducers are provided in the table below.

Table 5-1. 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 acetylsalicylic acid. If anticoagulation therapy needs to be initiated while on study treatment, the Investigator should consult with the Medical Monitor to determine if study treatment should be discontinued.

5.5. Accountability for GS-5829

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

GS-5829 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, and the quantity of study drug 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 Return or Disposal

Study drug 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. All study drug returned by the subject should be retained for review by the study site monitor prior to destruction.

Please see Section 9.1.7 for more information.

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 below.

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 assessment 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. Study Procedure Descriptions

During the treatment period, all visits may be performed within the specified window for that study visit (see Appendix 2). A subject is considered enrolled into the study once enrollment in the IxRS system is completed.

6.1.1. Informed Consent

All subjects must sign and date the most recent IRB/IEC-approved informed consent form before any study procedures are performed. CCI [redacted]

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

6.1.2. Medical & Medication History

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

6.1.3. Physical Examination

The Investigator or qualified designee will perform a physical examination at Screening and timepoints outlined in the Study Procedures Tables (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 which 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.

6.1.4. Vital Signs

Vital signs, including blood pressure, respiratory rate, pulse, and temperature will be measured at the time points listed in the Study Procedures Tables in Appendix 2. 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.

6.1.5. Electrocardiogram Assessment

Triplicate 12-lead ECGs reporting ventricular rate, PR, QRS, QT, and QTc intervals will be obtained at the timepoints outlined in the Study Procedures Tables (Appendix 2) 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 timepoint. Subjects should be resting quietly and free of distraction (e.g. tv, conversation) for 10 minutes prior to ECG collection and ECGs should be collected over a 5 minute window at each timepoint.

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.

6.1.6. Echocardiogram

Echocardiograms will be performed at the timepoints 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.

6.1.7. ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status will be performed at the timepoints listed in the Study Procedures Tables (Appendix 2). ECOG will be scored using the scale index in Appendix 8.

6.1.8. Prior and Concomitant Medications

At Screening, all medication taken up to 30 days prior to the screening visit will be 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 (eg, anti-emetics), and vitamins and minerals.

In addition, supportive therapies given during the course of the study (eg, blood transfusion, growth factor) should be collected and recorded on the eCRF.

6.1.9. Adverse Events

Subjects will be assessed for adverse events (AEs) per guidelines in the National Cancer Institute (NCI) CTCAE (version 4.03) at the timepoints outlined in the Study Procedures Tables (Appendix 2). Any AEs reported after informed consent is obtained and throughout the study will be recorded on the eCRF with appropriate source documentation. The site will contact the study subject by phone approximately 30 days after the last dose of study drug to assess AEs. Please refer to Appendix 6 for CTCAE grading criteria.

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

6.1.10. CT or MRI

CT scans will be obtained to document metastatic disease, identify target lesions as described in RECIST (version 1.1), and to assess response and disease progression. Patients with lymphoma will be assessed by Cheson Criteria (Appendix 5). Patients with Prostate Cancer will be assessed by radionuclide bone scan and CT scan (or MRI) of the chest, abdomen and pelvis. Response and disease progression for patients with prostate cancer will be assessed based on PCWG criteria (Appendix 4). 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 8 weeks before Day 1 if the scan was performed as part of standard medical practice) and at the timepoints outlined in the Study Procedures Tables (Appendix 2). Please refer to Appendix 3-Appendix 5 for additional information on RECIST (version 1.1), Cheson Criteria and PCWG2 Criteria.

The same radiographic procedure and specification (eg, the same contrast agent, slice thickness, etc.) used to define measurable lesions must be used throughout the study for each subject. Any subject with symptoms suggestive of disease progression should be evaluated for tumor response at the time the symptoms occur. Tumor burden will be characterized at Baseline and subsequent response assessments will be carried out according to the RECIST (version 1.1) criteria (solid tumors), Cheson Criteria (lymphoma) and PCWG Criteria (prostate).

For subjects in whom a radiologic CR is determined, a bone marrow biopsy may be required for complete assessment. In a subject who has a baseline bone marrow involvement with lymphoma or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of bone marrow lymphoma. In a subject who

has a baseline bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met. The bone marrow biopsy will be performed at the local lab.

6.1.11. Bone Scans (Group 2) Only

Subjects in Group 2 (breast cancer) will undergo radionuclide bone scan at Screening, as clinically indicated or to confirm complete response during the treatment period and at the end of treatment for sites of disease identified at Screening (unless disease progression has been confirmed elsewhere).

Group 2 Tumor Assessment Requirements:

Method	Screening	Treatment Period	End of Treatment Visit
CT or MRI of chest, abdomen, and pelvis	Required	Required	Required if not done within 4 weeks
CT or MRI of any other site of disease, as clinically indicated	Required	Required for sites of disease identified at screening	Required if not done within 4 weeks. Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Radionuclide bone scan (whole body) and confirmatory imaging in case of any hots spots (CT, MRI, or X-ray)	Required	As clinically indicated or to confirm complete response	Required if not done within 4 weeks. Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Photographs of all superficial lesions as applicable	Required	Required for sites of disease identified at screening	Required if not done within 4 weeks. Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere

6.1.12. PET/CT Scan

Subjects who are enrolled in Group 3 (DLBCL or PTCL) will undergo a positron emission tomography (PET) and CT scan at Screening and at Week 16 to evaluate response, unless the subject has demonstrated disease progression prior to this date.

6.1.13. Blood and Urine Samples

Blood and urine for laboratory safety tests will be collected according to the Study Procedures Tables (Appendix 2). The date and time of blood and urine collection will be recorded in the subject's source documentation. The date and time of previous GS-5829 dose will be recorded in the subject's source documentation on days where PK is collected. The tests will be analyzed using standard procedures. White blood cell (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 Study Day 1 / C1D1.

Day 1 pre-dose samples may be drawn up to 2 days prior to the Day 1 visit.

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

Table 6-1. Blood and Urine Samples Collected During the Course of the Study

Serum Chemistry	Hematology	Other
Sodium Potassium Chloride Glucose BUN Creatinine ALT AST Alkaline phosphatase Total bilirubin[a] Total protein Albumin Calcium Magnesium Phosphate Lactate dehydrogenase AAG	White Blood Cell (WBC) Count Hemoglobin Hematocrit Platelet Count Neutrophils (ANC) Lymphocytes Monocytes Basophils Eosinophils	GS-5829 concentration Serum and Plasma CCI Hepatitis B surface antigen (HBsAg) Hepatitis C (HCV) antibody 25-hydroxyvitamin D
	Coagulation	
	PT/INR aPTT Platelet Activation[b]	
Pregnancy Testing	**Urine**	
Serum Qualitative β-human chorionic gonadotropin (hCG) (females) Urine Pregnancy (females)	Urinalysis	

a Includes direct bilirubin
b platelet activation testing to be performed at specified sites

6.1.14. Pregnancy Test for Females of Childbearing Potential

All female subjects of childbearing potential (as defined in Appendix 7) will have a serum pregnancy test at Screening and a urine pregnancy test prior to Day 1 dosing, every 28 days thereafter, and at the EOT visit. The results must be confirmed as negative prior to continued administration of study drug.

6.2. Vitamin D Assessment for Patients in Group 2

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

6.2.1. Pharmacokinetic Samples

Plasma samples for GS-5829 PK will be collected (± 10 minutes) in cohorts 1-3 of Group 1 on Study Day 1 at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose and in cohorts 4-8 of Group 1 and all cohorts of Group 2 on Cycle 1 Day 1 at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Additional samples will be collected at 48 and 72 hours post-dose in dose levels 1 – 3 of Group 1 relative to first dose of GS-5829. Plasma samples for GS-5829 PK will be collected in all cohorts (Group 1 and Group 2) at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose relative to GS-5829 administration on Cycle 1 Day 8. Sparse PK samples will be collected in all cohorts (Group 1 and Group 2) at trough (20-26 hours post-dose) on Cycle 1 Day 4, 2 - 4 hours post-dose on Cycle 1 Day 15, and anytime post-dose on Day 1 of Cycles 2 through 6.

At one or more dose levels, PK samples will be collected on Day 1 of Cycle 2 at pre-dose (0 hr) and 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose. GS-5829 dose will be administered in fed state on Day 1 of Cycle 2.

Urine will be collected for GS-5829 PK in Group 1 cohorts 1-3 on Study Day 1 and in Group 1 cohorts 4-8 on Cycle 1 Day 1 at pre-dose, 0-6 hours, 6-12 hours, and 12-24 hours post-dose relative to first dose of GS-5829.

Subjects in the Group 3 lymphoma expansion will have PK drawn at pre-dose, 1, 2, 4, 6, and 24 hours post-dose on Cycle 1, Day 8. PK samples will also be drawn at pre-dose on Day 1 of Cycles 2, 4, and 6.

Plasma and urine concentrations of GS-5829 will be determined and PK evaluated. Plasma and urine concentrations of GS-5829 metabolite(s) may be determined and PK explored. Unbound concentrations of GS-5829 and/or metabolites may be determined. Plasma concentrations of fulvestrant, exemestane, or metabolites may be determined and PK explored.

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6.3.4. Unscheduled Procedures

Unscheduled procedures, including, but not limited to, vital signs, 12-lead ECG, and CT or MRI, will be recorded on the applicable eCRFs.

6.4. Post-treatment Assessments

6.4.1. Post-Study Phone Call

Subjects will be contacted by phone 30 days (± 7 days) after the last dose of GS-5829 to assess for AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information post-study anti-cancer therapies, surgeries, and date of definitive disease progression (if known).

6.5. Criteria for Discontinuation of Study Treatment

See Sections 3.4 and 3.5 for discontinuation criteria.

6.6. Replacement of Subjects

If a subject 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.

6.7. Dose Interruption and Reduction

The following are the guidelines for dose interruption and/or reduction. If an AE is attributed to study drug, the investigator's discretion will be used to determine if the drug not attributed to the AE will be withheld based on the investigator's assessment of risk-benefit of withholding the study drug.

6.7.1. GS-5829

For subjects without lymphoma, if at any time in the study a subject experiences a toxicity consistent with a Grade 4 DLT (see Section 3.2 for the definition of a DLT), GS-5829 treatment will be discontinued permanently, with the exception of Grade 4 neutropenia or thrombocytopenia. If a subject experiences Grade 4 neutropenia or thrombocytopenia or any other < Grade 4 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.

For subjects with lymphoma, if the toxicity is neutropenia or thrombocytopenia consistent with the definition of a DLT, the dose may be resumed at either one lower dose level, or the same dose with an alternative dosing schedule, which decreases the total amount of GS-5829 administered over a 28 day period to at least 25% less than the previous cohort (eg 14 days on and 7 days off). If the subject experiences a recurrence of a non-hematologic toxicity meeting criteria for DLT after restarting study drug at a lower dose or if the toxicity does not resolve within 28 days, treatment with GS-5829 will be discontinued. For subjects with lymphoma, 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% after discussion with the Gilead Medical Monitor.

Table 6-2. Dose Reduction of GS-5829

NCI CTCAE Grade	Recommendation	
	Group 1 and 2: Non-lymphoma GS-5829	**Group 3: Lymphoma 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 ≤ 1. If the toxicity resolves to ≤1 within 28 days, 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	Hold dosing with GS-5829 until the toxicity is resolved to ≤ 1. If the toxicity resolves to ≤1 within 4 days, the subject may resume dosing of GS-5829 at the same dose or a dose lower. 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. GCSF is allowed during dose interruption, but is not to be administered on the same day as GS-5829
Thrombocytopenia		
Grade ≤ 2 Thrombocytopenia	Maintain current dose level and schedule.	
Grade 3 Thombocytopenia	Hold dosing with GS-5829 until the toxicity is resolved to ≤ 1. If the toxicity resolves to ≤1 within 28 days, 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	Hold dosing with GS-5829 until the toxicity is resolved to ≤ 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. If the toxicity takes > 7 days to resolve to ≤ Grade 1, then the drug must be resumed at a lower dose or 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 ≤ 1. If the toxicity resolves to ≤1 within 28 days, 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. If it takes > 28 days, then GS-5829 will be permanently discontinued	Hold dosing with GS-5829 until the toxicity is resolved to ≤ 1 at which time the subject may either resume at a dose with is 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.

NCI CTCAE Grade	Recommendation	
	Group 1 and 2: Non-lymphoma GS-5829	**Group 3: Lymphoma GS-5829**
NON-HEMATOLOGICAL ADVERSE EVENTS		
Hepatic Adverse Events (elevations in ALT, AST or bilirubin)		
Grade 1 (ALT/AST ≤ 3xULN) (Bilirubin ≤ 1.5xULN)	Maintain current dose level and schedule.	
Grade 2 (ALT/AST > 3-5xULN) (Bilirubin>1.5 -≤ 3xULN)	Maintain current dose level and schedule. Monitor ALT, AST, ALP, and bilirubin at least 1x per 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 and or by a change in schedule which decreases total GS-5829 administered over a 28 day dosing period	
Grade 4	Permanently discontinue GS-5829	

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 Sciences Medical Monitor, GS-5829 may be re-started if the criteria for resuming treatment as described in Section 6.7.1 are met and the Investigator feels it is in the subject's best interest to do so.

7. ADVERSE EVENTS AND TOXICITY MANAGEMENT

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

7.1.1. Adverse Events

An adverse event (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 (see Section 7.6.1)
- 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 **serious adverse event** (SAE) or serious adverse drug reaction (SADR) 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.

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an AE in itself

- An SAE may occur even if the subject was not on study drug at the time of occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE

- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is a SAE

- "In-patient hospitalization" means the subject is formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department

- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms

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, and urinalysis) that require medical or surgical intervention or lead to study drug 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, ECG, 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 (eg, anemia), not the laboratory result (ie, decreased hemoglobin).

7.2. Assessment of Adverse Events and Serious Adverse Events

The investigator or qualified subinvestigator 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 subinvestigator is responsible for assessing the relationship to study drug therapy using clinical judgment and the following considerations:

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

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 6). 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 1 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

7.3.1. 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 eCRF: all SAEs and AEs related to protocol-mandated procedures.

7.3.2. Adverse Events

Following initiation of study medication, collect all AEs, regardless of cause or relationship, until 30 days after last administration of study drug 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.

7.3.3. Serious Adverse Events

All SAEs, regardless of cause or relationship, that occur 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 in the 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 drug, regardless of causality, should also be reported.

Investigators are not obligated to actively seek SAEs after the 30-day 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 study drug, 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.

7.3.4. 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 of the investigator's knowledge of the event 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.

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

- 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 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, 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 drug. 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.

7.4.1. Reporting of Adverse Events Relating to the Primary Endpoint and Other Anticipated Medical Events in the Study Population

Given the endpoints of the study, in order to maintain the integrity of the study, the following events that are assessed as unrelated to study drug will not be considered SAEs:

- Progression of disease
- Death related to progression of disease

Disease progression and death from disease progression should be reported as SAEs by the investigator only if it is assessed that the study drug 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.

7.5. Toxicity Management

Treatment-emergent toxicities will be noted by the Investigator and brought to the attention of the Gilead Sciences 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 Sciences 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. Reports of adverse reactions in infants following exposure from breastfeeding, and reports of adverse reactions associated with product complaints and reports arising from occupational exposure are also considered special situation reports.

- A pregnancy report is used to report any pregnancy in female subjects only, or female partners of male subjects on study
- 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 or 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 the 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 such. 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.

Pregnancies of female partners of male study subjects exposed to Gilead or other study drugs must also be reported and relevant information should be submitted to or Gilead DSPH using the pregnancy and pregnancy outcome forms within 24 hours. Monitoring of the subject should continue until the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Gilead DSPH.

Gilead DSPH: Fax: PPD
Email: PPD

Refer to Appendix 7 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 drug 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 the 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 objectives of this study are:

- Characterize the safety and tolerability of GS-5829 as a monotherapy in subjects with advanced solid tumors and lymphomas
- Determine the MTD or RDP2 of GS-5829 as a monotherapy in subjects with advanced stage solid tumors and lymphomas
- Characterize the safety and tolerability of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer
- Determine MTD or RDP2 of GS-5829 in combination with exemestane or fulvestrant in subjects with advanced estrogen receptor positive breast cancer

8.1.2. Primary Endpoint

The primary endpoint of this study is incidence of DLT as defined in Section 3.2.

8.1.3. Secondary Endpoint

Secondary endpoints of this study are:

- PK parameters (C_{max}, C_{tau}, AUC_{last}, AUC_{tau}, T_{max}, and $t_{½}$) for GS-5829.

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8.2. Analysis Conventions

8.2.1. Analysis Sets

8.2.1.1. Full Analysis Set (FAS)

The FAS includes all subjects who receive ≥ 1 dose of study drug (GS-5829, exemestane or fulvestrant). This analysis set will be used for subject characteristics and efficacy endpoints.

8.2.1.2. Safety Analysis Set

The Safety Analysis Set for this study will be the same as FAS since this study is a non-randomized study. This analysis set will be used for safety endpoints, study treatment administration and post-study therapy.

8.2.1.3. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who complete all treatment and safety procedures through Day 29, or experienced a DLT prior to Day 29. Determination of the MTD will be in DLT-Evaluable Analysis Set.

8.2.1.4. Pharmacodynamic and Pharmacokinetic Analysis Sets

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

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8.3. Data Handling Conventions

By-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, 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 study group, dose level, analysis set, and time point. As appropriate, changes from baseline to each subsequent time point will be described and summarized by study group and dose level. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized by study group and 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 study group and dose level for the Safety Analysis Set.

8.5. Efficacy Analysis

ORR and PFS will be listed only.

8.6. Safety Analysis

All safety data collected on or after the date that study drug (GS-5829, exemestane or fulvestrant) was first dispensed up to the date of last dose of study drug plus 30 days will be summarized by study group and dose level. Data for the pretreatment will be included in data listings.

8.6.1. Extent of Exposure

Descriptive information will be provided by study group and dose level regarding the number of doses of study drug prescribed (GS-5829, exemestane or fulvestrant), the total number of doses taken, the percent of expected doses taken, the number of days of study drug, and the number and timing of prescribed dose modification and interruptions.

GS-5829 compliance will be described by study group and dose level in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modification and interruptions).

8.6.2. Adverse Events

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. A treatment-emergent AE is defined as an AE that occurs or worsens in the period from the first dose of study drug (GS-5829, exemestane or fulvestrant) to 30 days after the last dose of study drug.

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. Summary tables will be presented to show the number of subjects reporting treatment-emergent AEs by severity grade and corresponding percentages. 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. AE descriptions will be presented by decreasing frequency for a given SOC and Preferred Term. Separate listings and summaries will be prepared for the following types of treatment emergent AEs:

- Study-drug-related (GS-5829, exemestane or fulvestrant) AEs
- AEs that are Grade ≥ 3 in severity
- AEs leading to study drug (GS-5829, exemestane or fulvestrant) interruption and/or dose modification
- AEs leading to study drug (GS-5829, exemestane or fulvestrant) discontinuation
- SAEs

8.6.3. Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data. 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, worsens by ≥ 1 grade in the period from the first dose of study drug (GS-5829, exemestane or fulvestrant) to 30 days after the last dose of study drug. If baseline data are missing, then any graded abnormality (ie, an abnormality that is Grade ≥ 1 in severity) will be considered treatment emergent.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE 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 programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc. Hematological and serum biochemistry and their changes from baseline will be summarized by study group, dose level, and visit. Summary tables will be presented 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 (eg, during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to the worst grade post-baseline. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline to the worst grade post baseline. Separate listings and summaries will be prepared for laboratory abnormalities that are Grade ≥ 3 in severity.

8.7. Pharmacokinetic Analysis

The concentration data of GS-5829 will be summarized by nominal sampling time using descriptive statistics. PK parameters (C_{max}, C_{tau}, AUC_{last}, AUC_{tau}, T_{max}, and $t_{½}$), will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, coefficient of variation (%) StD, median, minimum, and maximum). Plasma concentrations over time will be plotted in semi-logarithmic and linear formats as mean ± StD, and median (Q1, Q3) if applicable.

CCI [redacted]

[redacted]

8.9. Sample Size

The sample size of the study will be determined based on the number of dose levels evaluated and the emerging GS-5829-related toxicities. The study will consist of up to160 subjects.

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 Good Clinical Practice (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 subinvestigators 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 subinvestigator's) participation in the study. The investigator and subinvestigator 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. The investigator will not begin any study subject activities until approval from the IRB 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 on any modifications made to the protocol or any accompanying material to be provided to the subject after initial 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-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 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, CRF/eCRF, the study drug, 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, 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 study drug, 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, US, 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. 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 (eg, 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

Gilead recommends that used and unused study drug supplies be destroyed at sites if they have applicable standard operating procedure (SOP) to do so. The study monitor will evaluate each study center's study drug disposal procedures and provide appropriate instruction for destruction of unused study drug supplies, as needed. If the site has an appropriate SOP for drug destruction as determined by Gilead Clinical Operations or designee (per SOP-CR-23035), the site may destroy used (empty or partially empty) and unused study drug supplies in accordance with that site's approved SOP. A copy of the site's approved SOP will be obtained for central files. If the site does not have an acceptable SOP to destroy, or cannot due to other regulatory reasons, Gilead will provide instruction for the return if the study drug for disposal/destruction.

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, 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 in accordance with local requirements and receive documented approval before modifications can be implemented.

9.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency. 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 (see Section 9.1.4).

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, eg, 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 e protection of the subjects' interests.

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11. APPENDICES

Appendix 1. Investigator Signature Page

GILEAD SCIENCES, INC.
333 LAKESIDE DRIVE
FOSTER CITY, CA 94404

STUDY ACKNOWLEDGEMENT

A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5829 as a Monotherapy in Subjects with Advanced Solid Tumors and Lymphomas and in Combination with Exemestane or Fulvestrant in Subjects with Estrogen Receptor Positive Breast Cancer

GS-US-350-1599, Amendment 6, 20 June 2016

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

PPD

PPD

6-23-2016
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 Cycle Day	Screening Day 28	Study Day 1[a]	First 28 Days							Cycle 2 Day 1 and Every 2 weeks*	Cycle 2 Day 1 and Every 4 weeks	Every 8 weeks	EOT	30 day Safety Follow-up[k]
			Cycle 1 Day 1[b]	Day 2	Day 4	Day 8	Day 11	Day 15	Day 22					
Window (day)	-28	±0	±3	±0	±0	±1	±1	±2	±3	±7	±7	±7	±7	±7
Informed Consent	X													
Medical and Medication History[c]	X													
Physical Examination[d]	X	X	X	X	X	X	X	X	X	X			X	
Vital Signs[e]	X	X	X	X	X	X	X	X	X	X			X	
Oxygen saturation[f]	X	X	X	X	X	X	X	X	X	X			X	
Echocardiogram[r]	X										X		X	
Triplicate 12-lead ECG[g]	X	X	X			X					X		X	
Adverse events/ Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X			X	X
IP Dispensing		X[i]	X								X			
Exemestane or Fulvestrant[w] (Group 2 only)			X					X			X			
Dosing Diary Accountability			X	X	X	X	X	X	X	X				
IXRS Registration	X	X	X[j]							X			X	
CBC with differential	X[s]	X	X		X	X	X	X	X	X			X	
Chemistry[y]	X[s]	X	X		X	X	X	X	X	X			X	
Coagulation[q]	X[s]		X			X					X		X	
25-hydroxy vitamin D (Group 2 only)	X													
Urinalysis and Urine Chemistry		X	X			X			X	X			X	

Study Phase Cycle Day	Screening Day 28	Study Day 1[a]	First 28 Days							Cycle 2 Day 1 and Every 2 weeks*	Cycle 2 Day 1 and Every 4 weeks	Every 8 weeks	EOT	30 day Safety Follow-up[k]
			Cycle 1 Day 1[b]	Day 2	Day 4	Day 8	Day 11	Day 15	Day 22					
Window (day)	-28	±0	±3	±0	±0	±1	±1	±2	±3	±7	±7	±7	±7	±7
Pregnancy Test[l]	X	X	X[j]								X		X	
GS-5829 Intensive PK[m]		X	X			X					X[v]			
GS-5829 Sparse PK[m]					X			X			X[v]			
CCI														
CCI														
CCI														
Biopsies for Group 3 lymphoma expansion[x]	X									X[x]			X	
CT Scan w/Contrast or MRI[p]	X											X	X[p]	
PET Scan (Group 3 only)[z]	X													
Bone Scan(Group 2 only)	X												X	
ECOG Performance Status	X	X	X			X		X	X				X	
Treatment Response Assessment[t]												X	X	

* Day 1 of subsequent cycles.

a Study Day 1 is applicable to Cohorts 1-3 only of Group 1.

b Cycle 1 Day 1 occurs on Study Day 7 for subjects in Cohorts 1-3 of Group 1 and must occur at least 5 days, but no more than 9 days after Study Day 1. For Group 1 Cohorts 4 and higher and all cohorts of Group 2 the first day of study is Cycle 1 Day 1.

c Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

d Screening and End of Treatment Physical Examinations (PE) will be a complete PE. Beginning at Study Day 1 (Group 1 Cohorts 1-3) and C1D1 (all groups), a modified physical examination will be performed to monitor for any changes (e.g. lymph nodes, lung, cardiac, abdomen, skin, neurologic, and any systems, as clinically indicated). Weight (without shoes) should be measured at each PE. Height (without shoes) should be measured at screening only.

e Study Day 1 (Cohorts 1-3 of Group 1) and C1D1 (all groups) vital signs will be taken within 15 min pre-GS-5829 dose. C1D1 vitals will also be collected at 2 and 4 hours post dose (+/- 15 min); vital signs will be taken pre-dose only at all subsequent visits.

f Oxygen saturation will be tested with a pulse oximeter.

g ECG: At Screening, at predose on Day 1 of each Cycle starting with Cycle 2, and at EOT, a triplicate 12-lead ECG will be collected at a single timepoint. On Study Day 1(Cohorts 1-3 only) and C1D1 (Cohorts 4-8 only and all cohorts of Group 2), C1D8 (all cohorts) (at predose, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, and 12 hours post first dose +/- 20 min) and Day 1 of cycles 2-6 (at pre-dose). Subjects in the Group 3 lymphoma expansion will have ECGs collected at pre-dose, 1, 2, 4, 6, and 24 hours post-dose on Cycle 1, Day 8. ECGs will also be collected at pre-dose on Day 1 of Cycles 2, 4, and 6. ECGs should always be collected prior to PK (or any other blood draw) if they are to be collected at the same nominal timepoint. 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 timepoint.

h Adverse events will be assessed 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.

i Cohorts 1-3 of Group 1 will receive one dose of GS-5829 on Study Day 1, which will be administered in the clinic.

j Not applicable to subjects in Cohort 1-3 of Group 1.

k Subjects who miss the 30 day Safety Follow-up visit will be contacted by phone 30 days (± 2 days) after the last dose of GS-5829 to assess AEs.

l If applicable (females of child bearing potential). Serum pregnancy will be conducted at Screening. Urine pregnancy will be conducted pre-dose on Study Day 1/C1D1 of each cycle and at EOT.

m Plasma samples for GS-5829 PK will be collected (± 10 minutes) in cohorts 1-3 of Group 1on Study Day 1 at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose, and in cohorts 4-8 of Group 1 and all cohorts of Group 2 on Cycle 1 Day 1 at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. Additional samples will be collected at 48 and 72 hours post-dose in cohorts 1 – 3 of Group 1 relative to first dose of GS-5829. Plasma samples for GS-5829 PK will be collected in all cohorts (Group 1 and Group 2) at pre-dose (0 hr), 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hours post-dose relative to GS-5829 administration on Cycle 1 Day 8. Sparse PK samples will be collected in all cohorts (Group 1 and Group 2) at trough (20-26 hours post-dose) on Cycle 1 Day 4, 2 - 4 hours post-dose on Cycle 1 Day 15, and anytime post-dose on Day 1 of Cycles 2 through 6. Urine will be collected for GS-5829 PK in Group 1 cohorts 1-3 on Study Day 1 and in Group 1cohorts 4-8 on Cycle 1 Day 1 at pre-dose (0 hr), 0-6 hours, 6-12 hours, and 12-24 hours post-dose relative to first dose of GS-5829. Subjects in the Group 3 lymphoma expansion will have PK drawn at pre-dose, 1, 2, 4, 6, and 24 hours post-dose on Cycle 1, Day 8. PK samples will also be drawn at pre-dose on Day 1 of Cycles 2, 4, and 6

[redacted]

p Tumor evaluation by CT/MRI or applicable scan will be performed during screening (within 28 days of Day 1) and every 8 weeks thereafter for the first year and then every 12 weeks. A baseline scan within 8 weeks of Day 1 is acceptable. The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT/MRI or applicable scan should be conducted at the EOS visit if not conducted within the previous 4 weeks. Subjects with prostate cancer or in Group 2 should also undergo a bone scan. Scan at EOT visit is not necessary if restaging scan is performed within 4 weeks of the EOT.

q Includes PT/PTT.

r Echocardiogram will be performed at screening, C2D1, and EOT. MUGA is acceptable. The same modality must be used throughout study participation.

s Screening chemistry, hematology and coagulation to be collected within 7 days of Study Day 1/C1D1.

t Bone marrow biopsy is only to be performed to assess suspected CR, and only if the subject had lymphoma involvement of the marrow at baseline (or did not have a baseline marrow biopsy). After CR is determined, there is no need for any further bone marrow biopsy assessments.

[redacted]

v At one or more dose levels, GS-5829 will be administered in fed state on Day 1 of Cycle 2 and PK samples will be collected at pre-dose and 0.5, 1, 2, 3, 4, 6, 8, and 24 hours post-dose. In subjects where intensive PK is collected on Cycle 2, Day 1, sparse PK samples do not need to be collected at that visit.

w 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 Cycle 1 Day 1 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 Cycle 1 Day 1 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).

x Biopsies are requested from subjects with accessible disease and should be core needle or excision biopsies. The pre-treatment biopsy can be obtained any time after the last line of therapy and prior to the first dose, the Cycle 2 Day 15 biopsy can be obtained anytime between Cycle 2 Day 1 and Cycle 2Day 21. The EOT biopsy should be collected at progression only for subjects with progressive disease.

y AAG will be collected at Screening, pre-dose on C1D1 and C1D8 only. Ferritin and CRP will be collected pre-dose on C1D1 and Day 1 of every subsequent cycle.

z Subjects who are enrolled in Group 3 will undergo a baseline PET/CT scan and at Week 16 in the place of a CT scan if available.

Appendix 3. RECIST 1.1

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

E.A. Eisenhauer[a,*], P. Therasse[b], J. Bogaerts[c], L.H. Schwartz[d], D. Sargent[e], R. Ford[f], J. Dancey[g], S. Arbuck[h], S. Gwyther[i], M. Mooney[g], L. Rubinstein[g], L. Shankar[g], L. Dodd[g], R. Kaplan[j], D. Lacombe[c], J. Verweij[k]

[a]National Cancer Institute of Canada Clinical Trials Group, 10 Stuart Street, Queen's University, Kingston, ON, Canada
[b]GlaxoSmithKline Biologicals, Rixensart, Belgium
[c]European Organisation for Research and Treatment of Cancer, Data Centre, Brussels, Belgium
[d]Memorial Sloan Kettering Cancer Center, New York, NY, USA
[e]Mayo Clinic, Rochester, MN, USA
[f]RadPharm, Princeton, NJ, USA
[g]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA
[h]Schering Plough, Kenilworth, NJ, USA
[i]East Surrey Hospital, Redhill, Surrey, UK
[j]National Cancer Research Network, Leeds, UK
[k]Erasmus University Medical Center, Rotterdam, The Netherlands

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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 purposes, 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 $\geq$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. *Confirmation 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 interpretation of data. *Disease progression* is clarified in several aspects: in addition to the previous 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

* *Corresponding author:* Tel.: PPD fax: PPD
E mail address: PPD (E.A. Eisenhauer).
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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.

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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*

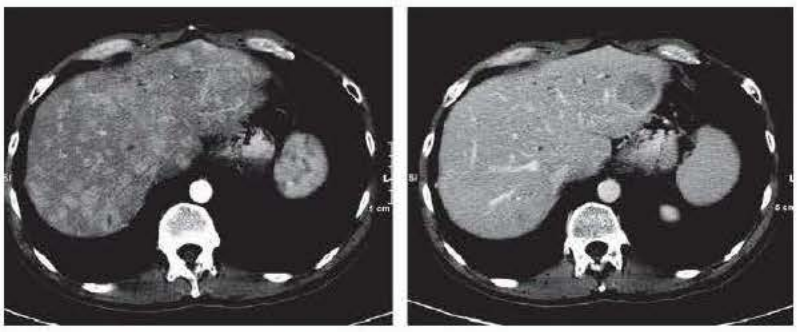

Fig. 1 – Difference in measurement/visualisation with different phases of IV contrast administration. Hypervascular metastases imaged in the arterial phase (left) and the portal venous phase (right). Note that the number of lesions visible differs greatly between the two phases of contrast administration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

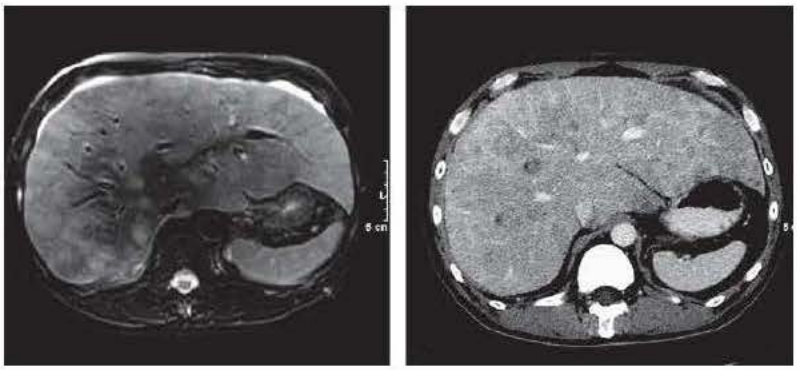

Fig. 2 – CT versus MRI of same lesions showing apparent 'progression' due only to differing method of measurement.

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

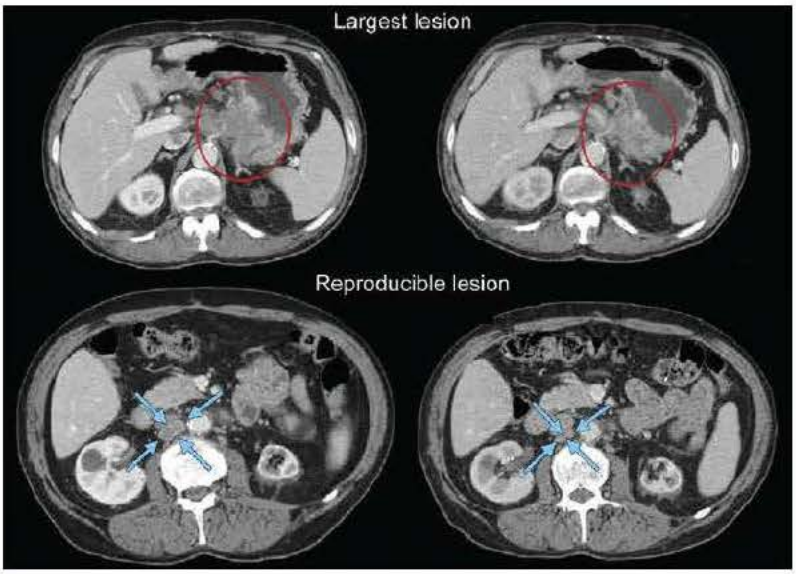

Fig. 3 – Largest lesion may not be most reproducible: most reproducible should be selected as target. In this example, the primary gastric lesion (circled at baseline and at follow-up in the top two images) may be able to be measured with thin section volumetric CT with the same degree of gastric distention 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).

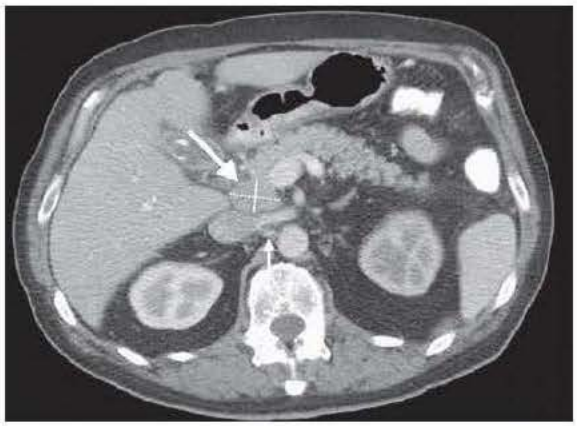

Fig. 4 – Lymph node assessment: large arrow illustrates a pathological node with the short axis shown as a solid line which should be measured and followed. Small arrow illustrates a non-pathological node which has a short axis <10 mm.

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.

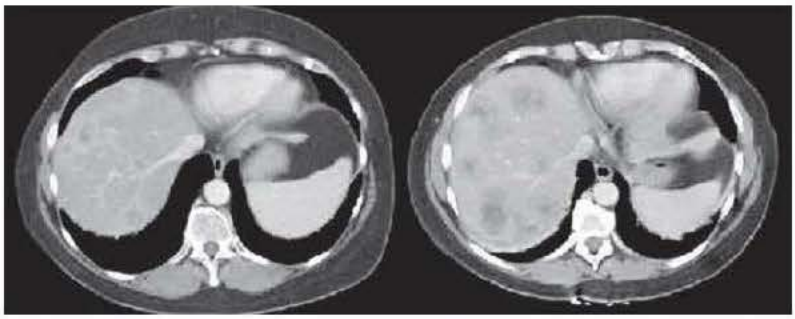

Fig. 5 – Example of unequivocal progression in non-target lesions in liver.

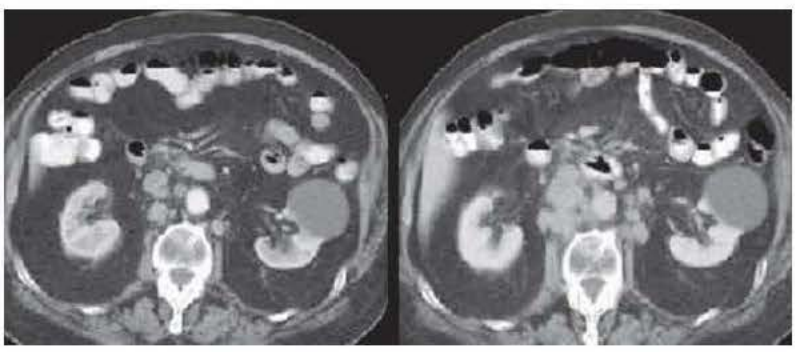

Fig. 6 – Example of unequivocal progression in non-target lesion (nodes).

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 4. Criteria for Progression in Castration-Resistant Prostate Cancer

Variable	Criteria
PSA	Ignore early rises (prior to 12 weeks) in determining PSA response For control/relieve/eliminate endpoints: Percent change from baseline at 12 weeks and maximal change at any time using a waterfall plot. Progression: Decline from baseline: record start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir and confirmed by a second value 3 or more weeks later. No decline from baseline: PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft tissue	Use RECIST with caveats: Only report changes in lymph nodes that were ≥ 2 cm in diameter at baseline Record changes in nodal and visceral soft tissue sites separately Record complete elimination of disease at any site separately Confirm favorable change with second scan
Bone	The appearance of ≥ 2 new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions The date of progression is the date of the first scan that shows the change

Appendix 5. Lymphoma Efficacy Assessments

Tumor Status Assessments

The determination of lymphoma response and progression will be based on standardized criteria {Cheson et al 2007, Owen et al 2013} as specifically modified for this study to reflect the biology of the diseases under study. During the course of the study, investigators will periodically assess the status of each subject's lymphoma.

Method of Assessment

In addition to clinical examination, imaging-based evaluation will be used in this study in all subjects enrolled. CT scan is the preferred method for radiographic tumor assessment. MRI scanning may be used at the investigator's discretion in subjects for whom this may be a preferred alternative to CT scanning; however, if MRI is performed, a non-contrast CT of the chest should also be performed. Contrast-enhanced scanning is preferred, but iodine-containing or gadolinium contrast material may be omitted in subjects for whom use of a contrast agent would be medically contraindicated. If available, positron emission tomography (PET) scan data will be considered in response and progression assessment; however, PET scanning will not be a required component of assessment in this study. As appropriate, bone marrow aspirate/biopsy information (eg, for confirmation of CR) will be also be considered. Clinical palpation, chest x-ray, ultrasound, endoscopy, laparoscopy, radionuclide scan, or tumor markers will not be considered for response assessment.

For radiographic assessments, the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) should be used to characterize each identified and reported lesion at baseline, while on study drug treatment and during follow-up. Furthermore, the use of IV contrast should be consistent across time points. In the event that the screening/baseline CT scan of the neck, chest, abdomen, and pelvis is performed without IV contrast, follow-up time points should also be performed without IV contrast.

All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification and for submission to the IRC.

Timing of Assessments

During screening, clinical and imaging-based tumor assessments should be performed within the specified screening period. On-study CT/MRI tumor assessments should be performed as indicated in Section 6.1.10. An end-of-study CT/MRI tumor assessment should be performed unless the subject already has radiographic confirmation of disease progression ≤4 weeks prior to study discontinuation. If a subject permanently discontinues study drug prior to objective documentation of lymphoma progression, investigators should continue further follow-up at ~8-week intervals until lymphoma progression is documented.

Identification and Follow-up of Tumor Lesions and Organomegaly

Index Lesions

Up to 6 lesions (eg, lymph nodes, liver or spleen nodules, and/or other circumscribed extra-nodal masses) should be selected as index lesions that will be used to quantitate the status of the disease during study. Ideally, the index lesions should be located in disparate regions of the body and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved.

Index lesions will be measured and recorded at baseline and at the stipulated intervals. The cross-sectional dimensions (the largest cross-sectional diameter, ie, the longest diameter [LD] × the longest perpendicular diameter [LPD]) will be recorded (in cm) for each index lesion. Using the LD and LPD, the product of the perpendicular diameters (PPD) for each index lesion will be calculated. The sum of the products (SPDs) for all index lesions will be calculated and recorded. The baseline SPDs will be used as references by which objective tumor response will be characterized during treatment. The nadir LDs of individual lesions and the nadir SPDs will be used as references by which objective tumor progression will be characterized during study. All PPD and SPD measurements will be reported in centimeters squared.

Nodal Index Lesions

A nodal mass may be selected as a nodal index lesion if it is both abnormal and measurable at baseline. A lymph node lesion is considered abnormal if it has a single diameter that is >1.0 cm and is considered measurable if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥1.0 cm and the LPD also being ≥1.0 cm.

Abnormal, measurable nodal lesions will be subcategorized as either large or small.

- Large nodal lesions have an LD that is >1.5 cm and an LPD that is ≥1.0 cm.
- Small nodal lesions have an LD that is >1.0 cm and ≤1.5 cm and an LPD that is >1.0 cm.

Index lesions measuring >1.5 cm in the LD, regardless of the measurement of the LPD, will be prioritized during baseline index lesion selection.

At follow-up time points, the SPD of all nodal index lesions will be considered. Because nodal index lesions that have one or both diameters >0 cm and <1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. Based on this convention, a CR may be achieved even if an SPD value is >0 cm^2 (ie, if all lymph nodes measure $\leq$1.0 cm^2).

New or enlarging nodal lesions that are still ≤1.0 cm by ≤1.0 cm will not be considered to represent recurrent disease or PD. A new node that measures >1.5 cm in any diameter or a new node that measures >1.0 cm to ≤1.5 cm in the LD and measures >1.0 cm in the LPD will be considered PD.

In cases in which a large lymph node mass has split into multiple components, only those elements that are >1.0 cm in at least 1 diameter will be considered abnormal and used in calculating the SPD. Components that are ≤1.0 cm in the LD are assumed to be normal lymph node structures. PD will not be based on the growth of a lesion sub-component until it meets the criteria for abnormal. Lesion sub-components that are abnormal (>1.0 cm in ≥1 diameter) will have the true PPDs calculated with the result used only for calculating an accurate nadir. Lesion sub-components that are normal (≤1.0 cm in the LD) will have the default PPD of 1.0 cm^2 (1.0 cm x 1.0 cm) stored only for the purposes of calculating the nadir value.

If lesions merge, a boundary between the lesions will be established so the LD of each individual lesion can continue to be measured. If the lesions have merged in a way that they can no longer be separated by this boundary, the newly merged lesion will be measured bi-dimensionally.

Extra-Nodal Index Lesions

An extra-nodal mass may be selected as an index lesion if it is both abnormal and measurable at baseline. An extra-nodal mass of any size is considered abnormal. It is considered measurable at baseline if it has 2 perpendicular diameters that can be accurately measured in cross section with the LD being ≥1.0 cm and the LPD also being ≥1.0 cm.

At follow-up time points, the PPD of each single extra-nodal index lesion and the SPD of all extra-nodal index lesions will be considered. Because extra-nodal index lesions that have one or both diameters >0 cm and < 1.0 cm cannot be reliably measured, a default value of 1.0 cm will be assigned for each diameter that meets these criteria and the resulting PPD will be used in SPD calculations. If an extra-nodal lesion is no longer clearly visible, it will be considered resolved and its PPD will be defined as 0 cm^2.

If an extra-nodal lesion that had resolved (ie, had a PPD of 0 cm^2) subsequently reappears unequivocally, the subject will be considered to have PD. A new unequivocal extra-nodal lesion of any size that appears at a site that was not previously involved with lymphoma and is discernible to the radiologist by CT scan will be considered PD.

Non-Index Lesions

Any other measurable and abnormal nodal or extra-nodal lesions not selected for quantitation as index lesions may be considered non-index lesions. In addition, non-measurable evidence of lymphoma such as abnormal, non-measurable nodal lesions, extra-nodal lesions with both diameters <1.0 cm, bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis of the skin or lung, abdominal masses that are not confirmed and followed by imaging techniques, cystic lesions, previously irradiated lesions, or lesions with artifacts may be considered as non-index disease.

If present at baseline, up to 6 non-index lesions should be recorded. Measurements are not required.

Non-index disease will be used as a general reference to further characterize regression or progression of lymphoma during assessments of the objective tumor response during treatment. These lesions should be followed as "present" or "absent".

Spleen and Liver

Qualitative assessments of the sizes of the spleen and liver will be performed. In addition, the presence or absence of splenic and/or hepatic nodules will be recorded.

Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies. Immunohistochemistry may be used to assess response if the sample is indeterminate by morphology.

In a subject who has a baseline bone marrow biopsy showing bone marrow involvement with lymphoma or does not have a baseline bone marrow examination, declaration of an on-study CR requires bone marrow biopsy documentation of the absence of bone marrow lymphoma. In a subject who has a baseline bone marrow biopsy showing no evidence of lymphoma, declaration of an on-study CR does not require bone marrow examination as long as other criteria for CR are met.

Definitions of Tumor Response and Progression

Responses will be categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). In addition, a response category of not evaluable (NE) is provided for situations in which there is inadequate information to otherwise categorize response status.

The best overall response will be determined. The best overall response is the best response recorded from the start of study drug until PD/recurrence (taking as reference for PD the smallest measurements recorded since study drug started). Subjects with a best overall response of NE will be included in the denominators in calculations of tumor response rate.

Response Categories

Complete Response

To satisfy criteria for CR, all of the following criteria must be met:

- No evidence of new disease
- Regression of all index nodal lesions to normal size (≤1.5 cm in the LD for nodes that were considered large at baseline and ≤ 1.0 cm in the LD and ≤1.0 cm in the LPD for nodes that were considered small at baseline) (see Nodal Index Lesions section for definitions of large and small nodes)
- Regression to normal of all nodal non-index disease

- Disappearance of all detectable extra-nodal index and non-index disease
- Normal spleen and liver size by imaging studies, no hepatic or splenic lymphoma nodules, and no new liver or spleen enlargement
- Morphologically negative bone marrow based on an adequate unilateral core biopsy if the sample is indeterminate by morphology, it should be negative by immunohistochemistry
- If PET performed (not required), no evidence of residual disease

Partial Response

To satisfy criteria for PR, all of the following criteria must be met as noted below:

- No evidence of new disease
- A ≥50% decrease from baseline in the SPD of the index lesions
- No increase in the size of non-index disease
- No increase in the size of the liver or spleen and no new liver or spleen enlargement
- Persistence of bone marrow involvement in a subject who meets other criteria for CR based on the disappearance of all nodal and extra-nodal masses
- If PET performed (not required):
  - Typically FDG-avid lymphoma: if no baseline PET scan or if the PET scan was positive before initiating study drug(s), the on-treatment PET is positive in ≥1 previously involved site. If baseline PET was performed and was negative, there is no new PET evidence of disease
  - Variably FDG-avid lymphoma/FDG-avidity unknown: if no pretreatment PET scan or if the pretreatment PET scan was negative for lymphoma, CT criteria should be used in assessing the tumor during study. If the PET scan was positive before initiating study drug(s), the on-treatment PET is positive in ≥1 previously involved site.

Stable Disease

To satisfy criteria for SD, all of the following criteria must be met:

- No evidence of new disease
- Neither sufficient tumor shrinkage from baseline to qualify for PR nor sufficient evidence of tumor growth to qualify for PD

Progressive Disease

The occurrence of any of the following events indicates progressive disease (PD):

- Evidence of any new disease that was not present at baseline:
  - A new node that measures >1.5 cm in LD and > 1.0 cm in the LPD.
  - A new node that measures >1.0 cm to ≤1.5 cm in the LD and >1.0 cm in the LPD
  - Unequivocal reappearance of an extra-nodal lesion that had resolved (ie, had previously been assigned a PPD of 0 cm^2)
  - A new unequivocal extra-nodal lesion of any size
  - New non-index disease (eg, effusions, ascites, or other organ abnormalities) of any size unequivocally attributable to lymphoma (usually requires PET, biopsy, cytology, or other non-radiologic confirmation to confirm disease attributable to lymphoma).

    Note: Isolated new effusions, ascites, or bone lesions are not sufficient evidence alone of PD unless histologically confirmed. In subjects with no prior history of pulmonary lymphoma, new lung nodules identified by CT are usually benign. Thus, a declaration of PD should not be made if this is the only manifestation of an apparently new lesion.
  - New or recurrent bone marrow involvement with lymphoma if the last prior bone marrow biopsy performed as part of the study (baseline or on-study) was negative for lymphoma
- Evidence of worsening of nodal or extra-nodal index lesions:
  - Increase from the nadir by ≥50% in the SPD of index lesions
  - Increase from the nadir by ≥50% in the LD of an individual node or extra-nodal mass that now has an LD of >1.5 cm and an LPD of > 1.0 cm
- Unequivocal increase in the size of non-index disease
- If PET performed (not required):
  - The appearance of any new lesion compatible with lymphoma with confirmation by other radiographic or histological modalities
  - The reappearance of any activity in a pre-existent lesion that meets size criteria for a new lesion on CT

Note: If there is uncertainty regarding whether there is definitive lymphoma progression, the subject should continue study drug and remain under close observation (eg, evaluated at scheduled intervals. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening lymphoma will not be considered definitive disease progression; in such subjects, both lymphoma -related and non-lymphoma -related causes for the constitutional symptoms should be considered. Transient worsening of disease during temporary interruption of study drug(s) (eg, for intercurrent illness) may also not indicate definitive disease progression. In these instances, CT/MRI should be attempted in order to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the time point at which progression was first objectively documented.

Non-Evaluable

In a subject who does not have evidence of PD, the occurrence of any of the following conditions indicates a response status of NE:

- There are no images or inadequate or missing images.

Note: A time-point will be considered to have a response of NE if any index lesion is missing. PD may be assigned at any time point regardless of the extent of missing index or non-index lesions. Missing non-index lesions will not impact the ability to assess for response or disease progression.

Appendix 6. Common Terminology Criteria for Adverse Events (CTCAE) v4.03

CTCAE v 4.03 can be accessed from the below link:

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

Appendix 7. 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.

Except in Group 2, subjects with breast cancer who are also receiving hormonal therapies, women are considered to be in a postmenopausal state when they are $\geq$ 60 years of age with cessation of previously occurring menses for $\geq$ 12 months without an alternative cause. In addition, women of any age with amenorrhea of $\geq$ 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, Group 2 subjects (breast cancer) who are pre/perimenopausal women are considered in a postmenopausal state due to treatment with the LHRH agonist goserelin. Patients 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 male born subject is considered to be fertile after the initiation of puberty unless permanently sterile by bilateral orchidectomy 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 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

  — Essure micro-insert system (provided confirmation of success 3 months after procedure)

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

Female 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) Contraception Requirements for Male Subjects

It is theoretically possible that a relevant systemic concentration may be achieved in a female partner from exposure of the male subject's seminal fluid. Therefore, male subjects with female partners of childbearing potential must use condoms during treatment and until 90 days after the end of relevant systemic exposure. Additional contraception recommendations should also be considered if the female partner is not pregnant.

Male subjects must also refrain from sperm donation during treatment and until at least 90 days after the end of relevant systemic exposure.

4) 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.

5) 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 8. 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 9. Exemestane (Aromasin®) Prescribing Information

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

Appendix 10. Fulvestrant (Faslodex®) Prescribing Information

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