TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I, first time in human, open-label, dose escalation study to investigate the safety, pharmacokinetics, and pharmacodynamics of anti-HER3 monoclonal antibody GSK2849330 in subjects with advanced HER-3 positive solid tumors

Compound Number: GSK2849330

Development Phase: I

Effective Date: 09-JAN-2015

Description: This is a Phase I, first time in human (FTIH), open-label, multi-center, dose-escalation study of the anti-HER3 monoclonal antibody, GSK2849330 administered to subjects with HER3-expressing or HER3 and NRG1-expressing solid tumors. The study will be conducted in two parts. Part 1 will include dose escalation and pharmacokinetic (PK)/ pharmacodynamic (PD) cohorts to evaluate safety, PK, and PD to guide selection of dose regimen(s) for Part 2. Part 2 will include at least 4 molecularly-defined tumor histology groups that will be studied to further characterize safety, PK, PD, and evaluate initial clinical activity of GSK2849330.

Protocol Amendment Number: 2

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Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2012N152466_00	2013-AUG-06	Original
2012N152466_01	2014-SEP-10	Amendment No. 1

Four molecularly-defined, tumor histology groups were added for study during Part 2: Group 1 will include subjects with HER3-expressing melanoma, Group 2 will include subjects with HER3-expressing gastric/gastroesophageal cancer, Group 3 will include subjects with HER3 and NRG1-expressing cancers of the head and neck, and Group 4 will include subjects with HER3 and NRG1-expressing non-small cell lung carcinoma (NSCLC).

Additional inclusion criteria for subjects in Part 2 were added to clarify the number of prior lines of therapy allowed for study entry and to require subjects to undergo pre and on-treatment tumor biopsies.

References to cohorts of subjects in Part 2 were removed and replaced with groups of subjects.

An additional cohort of subjects was added to Part 1. This cohort will receive weekly treatment with 30 mg/kg GSK2849330, with an option to reduce dosing frequency to every 2 weeks after 24 weeks.

The approximate number of subjects in Part 1 was changed from 10 to 13, to accommodate the additional weekly cohort. The anticipated number of subjects in Part 1 is now 34.

The rationale for adding a weekly dosing regimen was added.

Clarification regarding ECHO as the preferred method of LVEF assessment has been added.

The exclusion criteria for subjects with untreated brain or meningeal metastases and subjects treated for stable brain metastases were clarified.

PK sampling times were revised for subjects in Part 1enrolled under this amendment and for subjects enrolled in Part 2.

An Efficacy Population was defined.

Recent findings on the biodistribution of GSK2849330 in mice were added.

Preclinical and nonclinical findings on HER3 antibodies from recent studies and abstracts were added, including the rationale for the tumor types selected for Part 2.

The predicted half-life of GSK2849330 was changed from 8-9 days to 7 days at 30 mg/kg. The expected dosing frequency was changed from ≥2 weeks to 1-2 weeks.

Preliminary noncompartmental and population PK parameters for the 1.4 mg/kg, 3 mg/kg, and 10 mg/kg doses were added.

The definitions for subject and study completion were clarified.

The timing for disease assessment at the end of the study was clarified. The timing for serum samples for immunogenicity at the end of the study was clarified. Permitted and prohibited medications (growth factors, anticoagulants, and corticosteroids) were clarified. The recommendations for management of diarrhea were expanded. The requirement for a sample for selected cytokines in subjects experiencing suspected infusion-related reactions was added. The criterion for withholding of study treatment for QTc prolongation was clarified. Vials containing 5 mL of investigational product were introduced, and 1-mL vials will also continue to be used. References to "randomization" were changed to "enrollment." Several authors to the protocol were changed. Minor grammatical and formatting changes were made throughout the document.		
2012N152466_02	2015-JAN-09	Amendment No. 2
The inclusion criteria were modified for Molecularly Defined Tumor Histology Groups 1, 2 and 4 in Part 2 to remove the statement that subjects would be eligible for inclusion into the study if they had not received standard therapy when such therapy was not available to them commercially or via a clinical trial. The definition of DLT for subjects with thrombocytopenia was expanded to include Grade 3 events of thrombocytopenia associated with bleeding in addition to all Grade 4 events. The statements regarding obtaining paired tumor biopsies have been modified to include that all biopsies should be obtained from tumor easily accessible to biopsy using a procedure that is safe for the subject. The total volume of blood to be collected within the first 30 days of participation has been modified to account for the increased PK sampling. Inconsistencies were corrected in the Time and Events Tables in Section 7. Minor grammatical and formatting changes were made throughout the document.		

SPONSOR SIGNATORY

PPD

Jan. 9. 2015

Li Yan, MD. PhD
Clinical Development Lead
GlaxoSmithKline

PPD

Date

SPONSOR/MEDICAL MONITOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

Regulatory Agency Identifying Number(s): NA

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol HER117158

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:		
Investigator Address:		
Investigator Phone Number:		
Investigator Signature		Date

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LIST OF ABBREVIATIONS

ABC's	Airway, breathing, and circulation from basic life support
ADA	Anti-drug antibodies
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE(s)	Adverse event(s)
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-x)	Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-HCG	Beta-human chorionic gonadotropin
BP	Blood pressure
BQL	Below the quantification limit
BRAF	V-raf murine sarcoma viral oncogene homolog B1
BUN	Blood urea nitrogen
CAF	Cytokines and angiogenic factors
CBC	Complete blood count
CDC	Complement dependent cytotoxicity
CfDNA	Circulating cell free DNA
CI	Confidence Interval
CL	Systemic clearance of parent drug
Cmax	Maximum observed concentration
CPK	Creatinine phosphokinase
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CO_2	Carbon dioxide
CPMS	Clinical Pharmacokinetics Modeling and Simulation
CPR	Cardio pulmonary resuscitation
CR	Complete response
CRC	Colorectal cancer
CRM	Continuous reassessment method
CSR	Clinical study report
CT	Computed tomography
CV	Coefficient of variance
DLT(s)	Dose-limiting toxicity
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
EC	Ethics committee

ECG(s)	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDTA	Ethylenediamine tetraacetic acid
ECD	Extracellular domain
FACTS	Fixed and Adaptive Clinical Trial Simulator
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin-embedded
FSH	Follicle stimulating hormone
FTIH	First time in human
GCP	Good Clinical Practice
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HED	Human equivalent dose
HER3	Human epidermal growth Factor Receptor 3
HPLC	High-performance liquid chromatography
HIV	Human immunodeficiency virus
h/hr	Hour(s)
HR	Heart rate
HRT	Hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IDSL	International Data Standards Library
IEC	Independent ethics committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
INR	International normalization ratio
IP	Investigational product
IRB	Institutional Review Board
irCR	Immune related complete response
irPD	Immune-related progressive disease
irPR	Immune related partial response
irRC	Immune related response criteria
irSD	Immune-related stable disease
irSLD	Immune-related sum of lesion diameters
IV	Intravenous
IVRS	Interactive voice response system
kg	Kilogram

Km	Concentration at half maximal activity or rate
L	Liter
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LLN	Lower limit of normal
LSLV	Last subject's last visit
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
µg	Microgram
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
mL	Milliliter
µM	Micromolar
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRT	Mean residence time
MSDS	Material Safety Data Sheet
msec	Milliseconds
MTD	Maximum tolerated dose
MUGA	Multi gated acquisition scan
NA	Not applicable
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
N-CRM	Neuenschwander-Continuous Reassessment Method
NE	Not evaluable
ng	Nanogram
NK	Natural killer cells
NOAEL	No observed adverse effect level
NRG1	Neuregulin 1
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Overall response rate
OTC	Over the counter
PBL	Peripheral blood leukocytes
PBMC	Peripheral blood mononuclear cells
PCI	Potential clinical importance
PD	Progressive disease or pharmacodynamic
PES	Polyethersulfone
PFS	Progression-free survival
pg	Picogram
PGx	Pharmacogenetics

PK	Pharmacokinetic
pM	Picomolar
PO	Polyolefin
PR	Partial response
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog
PTT	Partial thromboplastin time
PVC	Polymerizing vinyl chloride
Q	Distributional clearance
qRT-PCR	Quantitative real time polymerase chain reaction
QTc	Corrected QT interval duration
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAMOS	Registration and Medication Ordering System
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
RTK(s)	Receptor tyrosine kinase(s)
SAE	Serious adverse event(s)
SC	Subcutaneous
SD	Stable disease or standard deviation
SPM	Study Procedures Manual
t1/2	Elimination half-life
τ	Dosing interval
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
US/USA	United States/United States of America
V	Volume of distribution
Vm	Maximal rate
WBC	White blood cells

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PROTOCOL SYNOPSIS

TITLE	A phase I, first time in human (FTIH), open-label, dose escalation study to investigate the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of anti-HER3 monoclonal antibody (mAb) GSK2849330 in subjects with advanced HER3-positive solid tumors
PROTOCOL NUMBER	HER117158
CLINICAL PHASE	I
COMPOUND(S)	GSK2849330
STUDY RATIONALE	GSK2849330 is a humanized glycoengineered IgG1/IgG3 mAb with enhanced Fc-effector function potency, directed against HER3 (ErbB3), a signaling and drug resistance target expressed on a wide range of solid tumors. This FTIH, open-label, dose escalation study will assess the safety, PK, PD, and preliminary clinical effect of GSK2849330 in subjects with HER3-expressing or HER3 and NRG1 expressing solid tumors.
STUDY OBJECTIVES, ENDPOINTS AND HYPOTHESES	Primary Objective Part 1: • To determine the safety and tolerability of GSK2849330 in subjects with advanced HER3-positive solid tumors. Primary Objective Part 2: • To evaluate the safety of GSK2849330 in a larger population of subjects in molecularly-defined tumor histology groups at the dose regimen(s) recommended for further exploration in Part 1. Secondary Objectives, Part 1: • To characterize the PK of GSK2849330 following intravenous (IV) administration. • To evaluate preliminary evidence of target engagement and PD effects of GSK2849330. • To determine the recommended dose regimen(s) of GSK2849330 for further exploration in Part 2. • To evaluate the immunogenicity of GSK2849330 following IV administration. Secondary Objectives, Part 2: • To evaluate preliminary evidence of clinical benefit. • To further characterize target engagement and PD

effects of GSK2849330.

- To further characterize the PK of GSK2849330.
- To characterize relationship between GSK2849330 PK, markers of target engagement, and/or PD markers.
- To evaluate the immunogenicity of GSK2849330 following IV administration.

Exploratory Objectives Part 1:

- To further evaluate preliminary evidence of target engagement and PD effects of GSK2849330.
- To explore relationships between GSK2849330 PK, markers of target engagement, and /or PD markers.
- To explore preliminary clinical tumor outcomes after treatment with GSK2849330.

Exploratory Objectives Part 2:

- To explore additional measures of clinical benefit.
- To further characterize target engagement and PD effects of GSK2849330.
- To explore the relationship between pre-treatment HER3 or HER3/NRG1 expression levels and clinical outcome.
- To identify molecular features potentially predictive of response to GSK2849330.

Pharmacogenetic (PGx) objectives Parts 1 and 2:

- To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.

Primary Endpoints Parts 1 and 2:

- Adverse events (AEs), serious adverse events (SAEs), dose limiting toxicities (DLTs), and changes in laboratory values, electrocardiograms (ECGs), and vital signs.

Secondary Endpoints Part 1:

- PK parameter values for GSK2849330.
- Total and phospho-HER3 from tumor tissue.
- Safety, tolerability, PK, and available PD data.
- Antibodies to GSK2849330 assessed in serum.

Secondary Endpoints Part 2:

- Overall response rate (ORR), tumor markers, and other measures of clinical benefit.

	• Total and phospho-HER3 from tumor tissue. • PK parameter values for GSK2849330. • Antibodies to GSK2849330 in serum. Exploratory Endpoints Part 1: • Pre- and post- treatment biomarkers (cells, proteins, ribonucleic acid [RNA] and/or deoxyribonucleic acid [DNA]) from circulation, skin, and/or tumor tissue. • Additional target engagement and PD markers in circulation, skin, and/or tumor. • Preliminary evidence of clinical benefit as assessed by ORR, tumor markers, and other measures of clinical benefit. Exploratory Endpoints Part 2: • Progression free survival (PFS), ORR according to immune-related response criteria (irRC) and modified Response Evaluation Criteria in Solid Tumors (mRECIST) where applicable, and other tumor markers and measures of clinical benefit. • Pre- and post- treatment biomarkers (cells, proteins, RNA and/or DNA) from circulation, and/or tumor tissue. • Pre-treatment HER3 expression or HER3 and NRG1 levels, efficacy outcome parameters. • Prediction analysis of biomarkers (cells, DNA, RNA or protein) in tumor, and/or circulation with efficacy endpoints. PGx exploratory Endpoints Parts 1 and 2: • Genetic variations in selected candidate genes, such as the FCγ-receptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.
STUDY DESIGN	This is a FTIH, open-label, dose-escalation study of GSK2849330 administered to subjects with HER3-expressing or HER3 and NRG1 expressing solid tumors. The study will be conducted in two parts. Part 1 will include dose escalation and PK/PD cohorts to evaluate safety, PK and PD to guide selection of dose regimen(s) for Part 2. The starting dose is 1.4 mg/kg, administered once-weekly, to be studied in a single patient (Cohort 1). If no DLTs are observed, dose escalation will progress to 3, 10, and 30 mg/kg, at a planned dosing frequency of

	every two weeks, followed by a 30 mg/kg weekly cohort, with three subjects studied at each dose level (except 1.4 mg/kg). In the cohort treated with 30 mg/kg/wk, the option to reduce the dosing frequency to every 2 weeks after 24 weeks of treatment may be exercised. The study team, in discussion with the investigator(s), may select lower doses or alternative schedules besides those listed above, based on emerging safety, tolerability, and PK findings. The occurrence of any DLTs will be evaluated using a Neuenschwander-Continuous Reassessment Method (N-CRM) to provide a model-based recommendation for dose escalation decisions. Dose escalation decisions, and any modifications to the proposed nominal dose levels or interval, will be based principally on review of safety data, including the output from the N-CRM, and will be supported by review of available PK and PD data. Once a dose escalation cohort has been filled, additional subjects may be enrolled into the PK/PD cohorts (at any dose level determined to be tolerable). Subjects in the PK/PD cohort must consent to a pre- and on-treatment biopsy, which will provide information on target engagement and tumor-based PD markers. Blood samples will be obtained to evaluate GSK2849330 PK and circulating PD markers. Safety, PK and PD data from Part 1 will be used to support the dose regimen selection for Part 2. In Part 2, at least 4 molecularly-defined tumor histology groups will be enrolled at the dose regimen(s) selected based on Part 1 data. The objective of Part 2 is to evaluate safety in a larger population in molecularly-defined, tumor histology groups of subjects at the recommended dose regimen(s). Part 2 will also evaluate PD markers in paired tumor biopsies and assess preliminary evidence of clinical benefit. Selection of the tumor types for focus in Part 2 was based on available preclinical and external data.
NUMBER OF SUBJECTS	Part 1: Approximately 13 subjects will be enrolled to complete the planned dose escalation. If DLTs are observed, additional subjects may be enrolled in dose escalation to establish the MTD or the dose for further exploration in Part 2, as guided by the N-CRM. A target maximum of 21 subjects with evaluable pre- and on-treatment tumor biopsies will be enrolled in the PK/PD

	cohorts. Additional subjects may be enrolled, if warranted, to provide sufficient safety, PK, or PD data to select the recommended dose for study in Part 2. Part 2: At least 4 molecularly defined tumor histology groups will be studied. A minimum of 12 and a maximum of 30 subjects will be enrolled in each of the groups. Futility criteria will be evaluated as data accrues, and enrollment in a group will be halted if futility criteria are met for that group.
INCLUSION/EXCLUSION CRITERIA	Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK study treatment that may impact subject eligibility is provided in the IB [GlaxoSmithKline Document number 2013N168399_01]. Deviations from inclusion/exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential. **Pre-screening Inclusion Criteria for Part 1** Subjects will be eligible for inclusion in pre-screening for the study (See Section 3.2) only if all of the following criteria apply: 1. Males and females ≥18 years of age (at the time consent is obtained). 2. Written informed consent provided. 3. Performance Status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 3). 4. Sufficient archival tumor specimen is available for HER3 IHC analysis, or subject is willing to undergo a fresh tumor biopsy (using a procedure that is safe for the subject) for HER3 IHC analysis (see Section 7.6.1.1 for details). 5. Histologically or cytologically confirmed diagnosis of one of the following solid tumor malignancies for which no standard therapeutic alternatives exist: • Bladder cancer • Breast cancer • Castrate-resistant prostate cancer

- Cervical cancer
- Colorectal cancer (CRC)
- Gastric cancer
- Hepatocellular carcinoma (HCC)
- Melanoma
- Non-small cell lung cancer (NSCLC)
- Ovarian cancer
- Pancreatic cancer
- Squamous cell cancers of the head and neck region (SCCHN)(including parotid and nasopharynx)

Pre-screening for Part 2

Subjects with melanoma, gastric/gastroesophageal cancer, head and neck cancer, or NSCLC who appear to meet all inclusion and exclusion criteria may be pre-screened for the study provided that sufficient tumor specimen either from archival Formalin-fixed, paraffin-embedded (FFPE) tissue or tissue obtained by biopsy (using a procedure that is safe for the subject) is available for analyzing HER3 by IHC or HER3 by IHC and NRG1 by RNA analysis.

Screening Inclusion Criteria for Parts 1 and 2

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. For subjects enrolled in Part 1: subjects must have tumors with documented HER3 expression (2+ or 3+) on the cell surface of the invasive component of the tumor using an analytically validated IHC assay by central laboratory (see Section 7.6.1.1 for details). Subjects enrolled in Part 2 must meet inclusion criterion 9 listed below.
4. ECOG performance status of 0 or 1 (see Appendix 3).
5. Adequate baseline organ function defined by:

SYSTEM	LABORATORY VALUES
Hematologic	
ANC	≥1.5 × 10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥75 × 10^9/L
PT/INR and PTT	≤1.3 × ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 × ULN
AST and ALT	≤2.5 × ULN
Renal	
Serum creatinine OR Estimated glomerular filtration rate or 24-hour urine creatinine clearance[a]	≤ ULN OR ≥50 mL/min
Cardiac	
LVEF	≥ 50% by ECHO or MUGA[b]

a. Estimated glomerular filtration as calculated by the Modification of Diet in Renal Disease (MDRD) equation (Appendix 4). When both a calculated and 24-hour creatinine clearance are available, the 24-hour value will be used.

b. ECHO is the preferred method. MUGA should be performed only if evaluation by ECHO is not available

6. If the subjects is female, she must be of non-childbearing potential, i.e., have a current tubal ligation, hysterectomy, ovariectomy or be post menopausal, or if she is of childbearing potential, she must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 11.1.1, from the time of the first dose of study treatment until 45 days or 5 half-lives (whichever is longer) after the last dose of study

treatment.

7. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1.2 from the time of the first dose of study treatment until 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment to allow for clearance of GSK2849330 from seminal fluid.
8. Subjects enrolled as part of the PK/PD cohort (Part 1) must agree to undergo pre- and on-treatment tumor biopsies, using a procedure that is safe for the subject.

Inclusion Criteria for Part 2 ONLY

As listed above for Part 1, with the exception of criterion 3 which should be replaced with the following criterion 9 and the addition of criteria 10 and 11.

9. For Group 1: subjects with previously treated, unresectable stage III or IV melanoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor using an analytically validated IHC assay by central laboratory.
    - Subjects must have received no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with BRAF V600 mutations who already received or were intolerant of prior BRAF inhibitor therapy may be included.
        - Subjects may be included if they had prior immune therapy, or were intolerant of prior immune therapy.

    For Group 2: Subjects with previously treated, unresectable stage III or IV gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor using an analytically validated IHC assay by central laboratory.

- Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
    - Subjects with HER2 positive disease may be included if they had already received prior anti-HER2 therapy, or were intolerant of prior anti-HER2 therapy.

For Group 3: Subjects with previously treated, unresectable stage III or IV cancers of the head and neck with documented HER3 expression on the cell surface of the tumor (≥1+) and NRG1 expression using analytically validated assays by central laboratory.

- Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
- Subjects with locoregional recurrences amenable to resection/surgery or additional radiation are excluded.

For Group 4: Subjects with previously treated, unresectable stage III or IV NSCLC with documented HER3 expression on the cell surface of the tumor (≥1+) and NRG1 expression using analytically validated assays by central laboratory.

- Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
- Subjects with anaplastic lymphoma kinase (ALK) translocation who already received or were intolerant of prior anti-ALK therapy may be included.
- Subjects with EGFR mutation positive disease (e.g., exon 19 deletion and exon 21 L858R) who already received or were intolerant of prior EGFR inhibitors may be included.

Additional tumor histology groups predicted to be sensitive to the study drug based on biomarkers (e.g.., HER3 mutations, NRG translocations) supported by preclinical or clinical data may be added based on emerging

data.

10. Subjects must have at least one measurable lesion per RECIST v1.1.

    NOTE: If the only site of measurable disease has been previously irradiated, documented progression of disease and a 4-week interval since completion of radiotherapy is required.

    NOTE: In subjects with ≥1 measurable lesion, a measurable lesion may be biopsied at Screening and Day 15; however that lesion must not be selected as a target lesion for disease assessment.

11. Subjects must have disease amendable to biopsy using a procedure that is safe for the subject, and agree to undergo pre- and on-treatment tumor biopsies (until the participating centers receive written notification from the Sponsor that paired tumor biopsies are no longer required).

Screening Exclusion Criteria for Parts 1 and 2

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subjects with leptomeningeal or brain metastases or spinal cord compression.
    - Subjects with untreated brain or meningeal metastases are not eligible (computed tomography [CT] scans are not required to rule this out unless there is a clinical suspicion of central nervous system [CNS] disease).
    - Subjects with treated and radiologic or clinical evidence of stable brain metastases (confirmed by 2 scans at least 4 weeks apart), with no evidence of cavitation or hemorrhage in the brain lesion are eligible providing that they are asymptomatic and do not require corticosteroids. Subjects are not permitted to receive enzyme inducing anti-epileptic drugs.
2. Prior HER3- directed treatment (HER2- or EGFR-directed treatment is acceptable).
3. Use of an investigational anti-cancer drug within

28 days or 5 half-lives, whichever is longer, preceding the first dose of GSK2849330 OR chemotherapy within the last 3 weeks (6 weeks for prior nitrosourea or mitomycin C) OR any major surgery, radiotherapy, immunotherapy or any other anti-cancer therapy within the last 4 weeks except as noted above.

4. Unresolved toxicity greater than NCI-CTCAE, version 4.0 [NCI, 2009] Grade 1 from previous anti-cancer therapy except alopecia and stable anemia (i.e., untransfused Hb ≥9.0 g/dL without the need for supportive transfusion within 2 weeks of screening) at the time of treatment allocation.
5. Known or suspected hypersensitivity reaction to prior biologic therapy (e.g., therapeutic monoclonal antibody) that in the opinion of the investigator is a contraindication to their participation in the study.
6. Current use of a prohibited medication or requires any of these medications during treatment (Section 10.2).
7. History or evidence of significant cardiovascular risk including any of the following:
    - LVEF<50%
    - A QT interval corrected for HR (QTc) ≥480 msec (≥500 msec for subjects with bundle branch block)
    - History or evidence of current clinically significant uncontrolled arrhythmias.

      Exception: Subjects with controlled atrial fibrillation for >30 days prior to enrollment are eligible.
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
    - History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).
8. Known Human Immunodeficiency Virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which will be

allowed).

9. Evidence of another active malignancy (excludes non-melanoma skin cancer). Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above.
10. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
11. Concurrent medical condition that in the investigator's opinion would jeopardize compliance with the protocol.
12. Lactating female.
13. Receiving chronic immunosuppressive therapies (includes daily steroid doses in excess of 20 mg/day of prednisone).

STUDY TREATMENT DOSE/ROUTE/REGIMEN	GSK2849330 will be given by IV infusion over 1 hour. If an infusion-related reaction occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator and/or medical monitor, and the subject will receive appropriate medical treatment. The infusion may be restarted according to the judgment of the investigator. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. For subsequent infusions, the investigator may provide premedication with antihistamines, acetaminophen, and/or corticosteroids and may reduce the starting infusion rate. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and remain on study at the discretion of the investigator and after discussion with the GSK medical monitor. In accordance with the preparedness for treatment of anaphylaxis, emergency resuscitation equipment, advanced cardiac life support equipment, and medications must be readily accessible during GSK2849330 administration.
SAFETY ASSESSMENTS	Measurements to evaluate safety will include weight, height, heart rate (HR), blood pressure (BP), temperature, echocardiogram (ECHO) or multi gated acquisition scan (MUGA) including calculation of left ventricular ejection fraction (LVEF), clinical laboratory tests, 12-lead ECG, ECOG performance status, and complete physical/neurological examination. AEs and laboratory results will be graded according to the NCI-CTCAE v4.0 [NCI, 2009]. Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1).
PHARMACOKINETIC/ PHARMACODYNAMIC ASSESSMENT(S)	For all subjects in the dose escalation cohorts in Part 1, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour and 6 hours after the end of infusion and at Day 8, Day 15, and Day 29 after the first dose of GSK2849330. If a subject's duration of infusion is 3 hours or longer, the 6 hour time point is optional. On days of dosing, the sample will be drawn pre-dose. Additionally the first subject in Cohort 1 will have PK samples taken at 24 hours (Day 2) and 72 hours (Day 4) after the end of infusion. For cohorts enrolled under Amendment 1 of this protocol, more frequent PK samples will be collected including:

	On Day 1 samples will be collected pre-dose and at 1 hour, 6 hours and 24 hours after the end of infusion. Pre-dose samples will be collected on Day 4, Day 8 and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85, and every 12 weeks thereafter For all subjects in the Part 1 PK/PD cohorts, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1 pre-dose and at 1 hour, 6 hours and 24 hours after the end of infusion. Pre-dose samples will be collected on Day 4, Day 8 and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85, and every 12 weeks thereafter. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. For the molecularly defined tumor histology groups enrolled in Part 2, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1 pre-dose and at 1 hour after the end of infusion; and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and every 12 weeks thereafter. For all subjects in Part 1 and Part 2, if treatment continues beyond 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken 45 days or 5 half -lives (whichever is longer) after the last dose of study treatment. Unless stated otherwise, on days of dosing, PK samples will be drawn pre-dose. Blood samples will also be collected pre-dose, during treatment, and at disease progression to explore circulating markers of PD activity according to the schedule outlined in the Time and Events Tables (Section 7.1). Samples for immunogenicity assessment will be obtained according to the schedule outlined in the Time and Events Tables. (Section 7.1).
CLINICAL ACTIVITY ASSESSMENT	Disease assessment will be performed every 8 to 9 weeks in all subjects (Parts 1 and 2). Disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Exploratory assessment of response according to irRC and mRECIST should also be recorded in applicable tumor types.

	Subjects whose disease responds [either complete response (CR) or partial response (PR)] should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated. RECIST 1.1 criteria will be employed to evaluate futility in Part 2.
TRANSLATIONAL RESEARCH	Comparative examination of pre-treatment, on- treatment and post-treatment markers (which may include DNA, RNA, protein, cell, blood or tissue examination) may be performed to uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK2849330, measure PD and/or response to treatment, or provide new insights into cancer and medically related conditions.
STATISTICAL METHODS	The total number of subjects in the Part 1 dose escalation will depend on the number of dose escalations needed, but the minimum number of subjects anticipated to complete dose escalation is 13. A target maximum of 21 additional subjects with evaluable pre- and on-treatment tumor biopsies may be enrolled in the PK/PD cohorts. Cohort size is based on feasibility and the objective to provide an initial characterization of safety and PK/PD information that will inform dose regimen selection for Part 2. In Part 2, at least 12 and up to 30 subjects will be enrolled in each group. Each group will include a futility analysis, whereby no additional subjects will be enrolled in a group if futility criteria are met, as defined in Section 13.6.2. The null hypothesis is: $H_0: p \leq 10\%$ The alternative hypothesis is: $H_A: p \geq 30\%$ Starting with a group of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 94% power. Group enrollment will be stopped early for futility if the predictive probability of success is less than 6%.The Bayesian Prior was Beta (0.2, 0.8), a weak prior with a mean response rate of 20%. The group outcome will be declared successful if the posterior probability of

	(P>0.10 | observed data) is ≥ 80%. Under the null hypothesis, the expected sample size is 20 subjects and the probability of early termination is 77%. Under the alternative hypothesis, the expected sample size is 29 subjects and the probability of early termination is 5%. The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2849330. Safety will be evaluated based on this analysis population. The **Efficacy Population** will consist of all subjects from the All Treated Population for whom at least one post-dose tumor assessment by CT scan has been performed. The **PK Population** will consist of all subjects from the All Treated Population for whom at least one post-dose PK sample is obtained and analyzed. Additional details of the statistical analysis plan will be provided in the reporting and analysis plan (RAP).

1. INTRODUCTION

1.1. Background

Many tumor types are characterized by dysregulation of the human epidermal growth factor receptor (HER) family of tyrosine kinase receptors, which includes HER1 (EGFR), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) [Kolibaba, 1997]. Both EGFR and HER2 are established pharmacologic targets in the treatment of cancer; emerging evidence also suggests that HER3 is an important therapeutic target. HER3 is expressed in a broad range of solid tumors, with varying prevalence depending on primary tumor type and histology. HER3 is a potent mediator of downstream signaling when heterodimerized with other receptor tyrosine kinases (RTK). The heterodimerization partners include other HER family members, such as EGFR, HER2, and HER4, as well as other RTK classes, including cMET and IGF-1R. Intracellular tyrosine sites on HER3 can be phosphorylated by an activated partner protein allowing recruitment of adaptor proteins and downstream activation of the MAPK and AKT signaling pathways.

While the HER3 gene is not frequently amplified in human cancers, HER3 protein expression has been associated with aggressive histopathological characteristics and poorer survival in various tumor types including melanoma, ovarian, gastric and colorectal carcinomas [Reschke, 2008; Tanner, 2006; Hayashi, 2008; Beji, 2011]. In melanoma cases with high HER3 expression as determined by immunohistochemistry (IHC), the probability of tumor-related death was almost three times higher than in cases with low HER3 staining [Reschke, 2008]. In gastric cancer, HER3 overexpression was associated with a significantly worse survival (P =0.0000) and was an independent prognostic factor in a multivariate analysis (hazard ratio 2.382; p = 0.048) [Hayashi, 2008] In a recent meta-analysis that included 12 clinical studies (3 colorectal cancer [CRC], 2 gastric cancer, 2 breast cancer, and 1 each for melanoma, ovarian cancer, head and neck cancer, pancreatic cancer, and cervical cancer) HER3 over-expression, as determined by immunohistochemistry (IHC), was significantly associated with poorer overall survival at both 3 and 5 years [Ocana, 2013]. Recently, somatic mutations of HER3 have been described in ~11% of screened gastric and colon cancers [Jaiswal, 2013]. These mutations promote oncogenic signaling in a ligand-independent manner *in vitro*, suggesting functional relevance, and provide a potential targeted population for clinical studies.

HER3 is also increasingly recognized as an important mediator of drug resistance following treatment with inhibitors of multiple key cancer pathways, including EGFR, HER2, IGF-1R, PI3K, RAF and MAPK [Amin, 2010; Zhang, 2014; Kugel, 2014]. This role has important implications for the potential utility of anti-HER3 therapeutics in combination with inhibitors of these pathways. The development of therapeutic agents targeting HER3, either as single agents or in combination with other anti-cancer agents, may provide clinical benefit for subjects with cancers exhibiting HER3 expression.

1.2. GSK2849330

1.2.1. GSK2849330 - Background

An overview of the pre-clinical studies of GSK2849330 is provided below. Detailed information concerning the biology, pharmacology, pharmacokinetics (PK), and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document number 2013N168399_01].

GSK2849330 is a humanized IgG1/IgG3 monoclonal antibody (mAb) with a molecular mass of approximately 145 kDa. GSK2849330 selectively binds HER3 at Domain III which resides in the extracellular domain (ECD) of the protein. HER3 sequences are 99% identical (99% homologous) between human and cynomolgus monkey, and 91% identical (94% homologous) between human and rat or mouse. The binding affinity of GSK2849330 for HER3 across these species is comparable: human: 2.1 nM; cynomolgus monkey: 1.7 nM; mouse: 4.1 nM; rat: 3.4 nM. In addition to directly blocking the heregulin (NRG1) ligand binding to the HER3 ECD, the antibody also sterically prevents the receptor from adopting the extended conformation that is required for dimerization, a prerequisite for receptor activation.

GSK2849330 is a glycoengineered antibody with enhanced potency for antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC causes tumor cell lysis upon binding of antibody to target, followed by engagement of cytotoxic T-cells and natural killer (NK) effector cells via their FcγRIIIA receptors. Perforin, granulysin and serine proteases released from cytoplasmic granules within cytotoxic T-cells and NK cells produce tumor cell lysis. CDC, considered one of the most powerful cell-killing mechanisms of antibodies [Walport, 2001], results from assembly of the 'membrane attack complex' that punches holes in the target cell membrane leading to tumor cell lysis. Compared with a wild-type antibody, GSK2849330 has a 16-18 fold greater binding affinity to human FcγRIIIA (responsible for initiating ADCC) and a 17-fold higher affinity to human complement protein (C1q, responsible for initiating CDC). These increased binding affinities translated to enhanced potency of GSK2849330, compared to wild type antibody, in cell based assays for ADCC and CDC (see IB for details).

In summary, there are three main potential antitumor modes of action when GSK2849330 is administered as monotherapy: a) inhibition of signaling; b) ADCC and c) CDC. The latter two mechanisms provide an opportunity for differentiation from non-ADCC and CDC- enhanced HER3-directed mAbs in clinical development, based on direct killing of both dividing and non-dividing cells, which may be independent of inhibition of downstream signaling.

1.2.2. Pre-clinical Pharmacokinetics of GSK2849330

The preclinical PK of GSK2849330 has been investigated following intravenous (IV) administration in the mouse, monkey and rat. Details of the preclinical PK are provided in Section 3.6.3 and the IB [GlaxoSmithKline Document number 2013N168399_01].

1.2.3. Nonclinical Safety of GSK2849330

GSK2849330 toxicology studies were conducted in rats and monkeys, which were shown to be suitable species based on similar HER3 tissue expression, protein sequence homology, and binding affinity of GSK2849330 for HER3. IHC assessment of HER3 distribution in normal human tissues showed specific positive staining in the majority of tissues examined and was characterized by cytoplasmic staining of epithelial cells, nerve fibers/ganglia, and focal areas of cells in the spleen. Membrane staining of epithelial cells was observed inconsistently only in the mammary gland ducts, cornea, esophagus, epidermis, tonsil, cervix and endometrium. These results are consistent with results previously published where HER3 expression in human tissue was examined by IHC [Prigent, 1992] and through the evaluation of a microarray gene expression database [Gene Logic, Ocimum Biosolutions, LLC, Houston, TX, USA, Uhlen, 2010]. Furthermore, HER3 receptor protein has been shown by IHC to be associated with peripheral nerves and Schwann cells in particular [Carroll, 1997]. A similar distribution of epithelial cell and peripheral nerve HER3 expression was observed in tissues from untreated monkeys using IHC.

In the good laboratory practice (GLP) toxicology studies, GSK2849330 was well tolerated in rats and monkeys following weekly IV dosing for 1 month up to and including the top doses studied, 500 mg/kg and 300 mg/kg, respectively.

In monkeys, dose-dependent, abnormal fecal consistency (beginning following a single dose) occurred at ≥30 mg/kg/dose, continued into a 4-week recovery period in monkeys given 300 mg/kg/dose and was not associated with effects on food consumption or body weight. Mucosal ulcers (mild, multifocal), associated with neutrophilic inflammation, occurred in the cecum and colon in one of three females given 300 mg/kg/dose after 4 weekly repeat doses. No ulcerations of the cecum/colon were present in recovery monkeys; however, reversibility was not clearly demonstrated based on low incidence and persistent systemic exposure in the study. Abnormal fecal consistency and ulceration of the cecum/colon occurred at 1X and10X the maximum planned clinical dose (30 mg/kg), respectively.

In rats, decreases in prostate weight (with no microscopic correlate) and minimal to marked lobuloalveolar atrophy of the male mammary gland were observed at doses ≥5 mg/kg/dose. There was a minimal decrease in the mean serum testosterone and luteinizing hormone (LH) concentrations in male rats given 500 mg/kg/day. Decreases in prostate weight and serum testosterone/LH concentrations were reversed following a 4-week off-treatment period, and lobuloalveolar atrophy was persistent over the same period, in rats given 500 mg/kg/dose. In the male rat, both the prostate and mammary gland are androgen dependent tissues and the mammary gland is unique in that it undergoes androgen-dependent development and maintains a sexually dimorphic appearance [Lucas, 2007]. Changes in the prostate and male rat mammary gland of rats are likely pharmacologically mediated effects of HER3 receptor inhibition with either direct effects on cell growth and differentiation or effects mediated by inhibited or reduced androgen receptor signaling. The effect on male rat mammary gland is not considered to be relevant to the risk assessment for the adult human male or female that is not pregnant or lactating.

In the 4-week GLP toxicity study in monkeys, there were no GSK2849330-related effects on cardiac histology or cardiovascular measurements (qualitative electrocardiogram [ECG] waveform evaluation including corrected QT interval duration [QTc], echocardiographic measures of left ventricular structure and function and clinicopathologic evaluation of serum cardiac troponin I). Additionally there were no GSK2849330-related effects on serum cardiac troponin I or cardiac histology in the 4-week GLP toxicity study in rats.

In the 4-week GLP toxicity study in monkeys, anti-drug antibodies (ADA) were detected in 4 of 6 monkeys given 3 mg/kg/dose with an associated decrease in GSK2849330 exposure. In monkeys given 30 mg/kg/dose, ADA were detected in 1 of 6 monkeys at the end of a 6-week off-treatment period. In the 4-week GLP toxicity study in rats, ADA were detected in 5 of 6 rats given 5 mg/kg/dose at the end of a 6-week off-treatment period, where GSK2849330 exposure was not clearly affected. ADA were not detected in monkeys at doses ≥30 mg/kg/dose during the dosing period and were not identified during the dosing period in rats at any dose; therefore, sufficient exposure to GSK2849330 was maintained at the no observed adverse effect level (NOAEL) doses and above in the toxicology studies in monkeys and rats to assess for potential adverse effects. Induction of antibody formation in animals when using humanised protein is not predictive of a potential for antibody formation in humans.

The NOAEL in the monkey was 30 mg/kg/week (area under the concentration-time curve from zero to 168 hr [AUC_{0-168}] 102 mg.h/mL, range 68.5 to 115 mg.h/mL; maximum observed concentration [C_{max}] 1.26 mg/mL, range 1.10 to 1.39 mg/mL (gender-averaged based on Week 4 values)]. The NOAEL in the rat was 500 mg/kg/week [AUC_{0-168} 573 mg.h/mL, range 465 to 617 mg.h/mL; C_{max} 13.1 mg/mL, range 11.4 to 15.1 mg/mL (gender-averaged based on Day 22)].

1.2.4. Pre-clinical Activity and Pharmacodynamics of GSK2849330

1.2.4.1. In vitro studies

GSK2849330 is a potent antagonist of HER3 signaling as evidenced by its ability to inhibit NRG1-induced HER3 receptor phosphorylation in various cancer cell lines (half maximal inhibitory concentration [IC_{50}] 2.5-30 ng/mL [17.2-207 pM]), and NRG1-induced AKT phosphorylation in BxPC3 pancreatic cancer cell lines (IC_{50} 11 ng/mL [76 pM]). GSK2849330 is also able to inhibit NRG1-induced proliferation of BxPC3 cells in a concentration dependent manner (33% inhibition at 10 μg/mL [69 nM]).

ADCC assays using both high- and low-expressing HER3 human target cells demonstrated the increased potency and target cytotoxicity achieved with the ADCC-enhanced GSK2849330 compared to the WT parental antibody. For example, when a CHL-1 human melanoma cell line was used as target cells and human peripheral blood leukocytes (PBLs) as effector cells, the potency of GSK2849330 was 245-764 pg/mL (1.7-5.3 pM) versus 35 ng/mL (241 pM) for the WT antibody. The efficacy of GSK2849330 was also tested against cynomolgus HER3 (transduced into human HEK293 cells) in combination with cynomolgus PBLs as effector cells. In this assay,

GSK2849330 had IC_{50}=454-910 pg/mL (3.76-7.5 pM) whereas parental WT antibody had IC_{50}=4.2-5.5 ng/mL (29-38 pM).

GSK2849330 caused concentration-dependent complement-mediated cell lysis of HEK293 cells transduced with full length human HER3. CDC activity level was proportional to HER3 protein expression on the cell surface, suggesting threshold HER3 expression amounts may be required to engage effective CDC activity. The level of ADCC killing may also be related to the amount of HER3 expression on the cell membrane [Bossenmaier, 2012].

1.2.4.2. Studies *in vivo*

GSK2849330 or variants have been evaluated for anti-tumor activity in melanoma and pancreatic cancer cell line xenograft tumor models Twice weekly IP dosing with GSK2849330 at 0.5 to 50 mg/kg/dose, resulted in dose-dependent and statistically significant decreases ($p<0.001$ at $\geq$5 mg/kg) in tumor growth rates in a human melanoma cell line (CHL-1) subcutaneous xenograft model. Significant inhibition of tumor growth was also observed in subcutaneous pancreatic (BxPC3) cancer cell line xenograft models and in a syngeneic mouse melanoma (lung colonization) model. Since xenograft studies were carried out in immune-compromised CB17 SCID mice, which lack T and B cells, and the disposition and nature of Fcγ receptor subtypes in mouse are different to that observed in human [Smith, 2012], the effects of GSK2849330 on tumor growth in these mouse models are expected to result mainly from HER3 signaling inhibition (e.g., ligand blocking/inhibition of heterodimerization) rather than an effect of the other potential (cell killing) modes of action for GSK2849330. In agreement with this hypothesis, GSK2849330 and Fc-disabled variant of GSK2849330 showed similar tumor growth inhibition in CHL-1 tumor xenograft.

1.3. HER3 antibodies in Clinical Trials

Although this is the FTIH study for GSK2849330, there is relevant experience for targeted inhibition of HER3 in cancer subjects. Initial clinical data from Phase I studies of other monoclonal antibodies targeting HER3 have been reported. Two of the antibodies, MM-121 and U3-1287, are non-enhanced human or humanized IgG1 antibodies. One antibody, RG7116, is a glycoengineered humanized IgG1 antibody reported to have enhanced potency for ADCC activity. Another antibody, LJM716, is a fully human monoclonal antibody that inhibits both ligand-dependent and -independent activation of HER3. These antibodies have been administered in clinical trials at doses up to 40 mg/kg weekly IV without dose limiting toxicities (DLTs) and without reaching a maximum tolerated dose (MTD). The majority of adverse events (AEs) have been Grade 1 or 2 with GI toxicity and fatigue predominating across studies. Infusion reactions, although seen, were reportedly not severe [Arnedos, 2013 Lorusso, 2013, Meulendijks, 2013, Denlinger, 2011, Reynolds, 2014].

1.4. Summary of Risk Management

The anticipated AEs based on preclinical studies include:

Gastrointestinal (GI): Mild GI hazard/diarrhea (multifocal ulceration of the cecum and colon, and abnormal fecal consistency), was observed as discussed in Section 1.2.3. High-grade diarrhea has not been reported with other HER3-targeting agents that have already been tested in the clinic; however precautions have been added to the protocol in the event that unexpected GI toxicity is observed with GSK2849330. Medical history, physical examination and clinical laboratory assessments will be used to identify and assess toxicity in the GI tract. Supportive therapy will be provided according to the diarrhea management guidelines provided in Section 3.9.3 and standard medical practice. Treatment with GSK2849330 will be withheld for clinically significant toxicity.

Prostate: Reversible decreases in prostate weight and serum testosterone and LH concentrations were seen in rats given GSK2849330. Decreases in prostate weight may represent inhibited or reduced androgen receptor activation. No clinical consequences are expected from decreased prostate volume and no clinical signals relating to prostate have emerged from ongoing studies with other agents that target HER3. However, serial measurement of testosterone and LH will be performed in male study subjects to explore for clinical correlation.

Further information on these potential risks can be found in Section 1.2.3 and the IB for GSK2849330 [GlaxoSmithKline Document number 2013N168399_01]

2. OBJECTIVE(S) AND ENDPOINT(S)

2.1. Part 1: Dose Escalation and PK-PD Cohorts

Objective	Endpoint
Primary	
• To determine the safety and tolerability of GSK2849330 in subjects with advanced HER3-positive solid tumors.	• AEs, serious adverse events (SAEs), DLTs, and changes in laboratory values, electrocardiograms (ECGs), and vital signs.
Secondary	
• To characterize the PK of GSK2849330 following IV administration.	• PK parameter values for GSK2849330.
• To evaluate preliminary evidence of target engagement and PD effects of GSK2849330	• Total and phospho-HER3 from tumor tissue
• To determine the recommended dose regimen(s) of GSK2849330 for further exploration in Part 2.	• Safety, tolerability, PK, and available PD data.
• To evaluate the immunogenicity of GSK2849330 following IV administration.	• Antibodies to GSK2849330 assessed in serum
Exploratory	
• To further evaluate preliminary evidence of target engagement and PD effects of GSK2849330.	• Pre- and post- treatment biomarkers (cells, proteins, ribonucleic acid [RNA] and/or deoxyribonucleic acid [DNA]) from circulation, skin, and/or tumor tissue.
• To explore relationships between GSK2849330 PK, markers of target engagement, and /or PD markers.	• GSK2849330 concentration-time profile and PK parameters, target engagement and PD markers in circulation, skin, and/or tumor
• To explore preliminary clinical tumor outcomes after treatment with GSK2849330.	• Preliminary evidence of clinical benefit as assessed by overall response rate (ORR), tumor markers, and other measures of clinical benefit
Pharmacogenetic (PGx) Exploratory	
• To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.	• Genetic variations in selected candidate genes, such as the FCγ receptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.

2.2. Part 2: Molecularly Defined Tumor Histology Groups

Objective	Endpoint
Primary	
• To evaluate the safety of GSK2849330 in a larger population of subjects in molecularly-defined tumor histology groups at the dose regimen(s) recommended for further exploration in Part 1.	• AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs.
Secondary	
• To evaluate preliminary evidence of clinical benefit.	• ORR, tumor markers, and other measures of clinical benefit.
• To further characterize target engagement and PD effects of GSK2849330.	• Total and phospho-HER3 from tumor tissue.
• To further characterize the PK of GSK2849330.	• PK parameter values for GSK2849330.
• To characterize the relationship between GSK2849330 PK, markers of target engagement, and/or PD markers.	• PK parameter values for GSK2849330
• To evaluate the immunogenicity of GSK2849330 following IV administration.	• Antibodies to GSK2849330 in serum
Exploratory	
• To explore additional measures of clinical benefit.	• Progression free survival (PFS), ORR according to immune-related response criteria (irRc) and modified Response Evaluation Criteria in Solid Tumors mRECIST where applicable, and other tumor markers and measures of clinical benefit
• To further characterize target engagement and PD effects of GSK2849330.	• Pre- and post- treatment biomarkers (cells, proteins, RNA and/or DNA) from circulation and/or tumor tissue.
• To explore relationship between pre-treatment HER3 or HER3/NRG1expression levels and clinical outcome.	• Pre-treatment HER3 expression or HER3 and NRG1 levels, efficacy outcome parameters.
• To identify molecular features potentially predictive of response to GSK2849330.	• Prediction analysis of biomarkers (cells, DNA, RNA or protein) in tumor, and/or circulation with efficacy endpoints.

Objective	Endpoint
Pharmacogenetic (PGx) Exploratory	
• To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.	• Genetic variations in selected candidate genes, such as the FCγ receptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.

3. INVESTIGATIONAL PLAN

3.1. Discussion of Study Design

Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Section 7.1) are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This is a Phase I, FTIH, open-label, multi-center, dose-escalation study of the anti-HER3 antibody, GSK2849330, in subjects with advanced solid tumors expressing HER3 (see Inclusion Criteria 3 and 9). The study will be conducted in two parts as depicted below.

Part 1
Dose Escalation Cohorts
To determine the safety, tolerability, PK and preliminary PD of GSK2849330, in support of selection of the recommended dose(s) and regimen(s) for further exploration in subjects with advanced solid tumors with HER3 expression

PK/PD Cohorts

Subjects that agree to give pre- and on- treatment tumor biopsies will be enrolled in the PK/PD cohorts to support selection of the recommended dose(s) and regimen(s) for Part 2. Up to 3 subjects with evaluable pre- and on-treatment tumor biopsies will be enrolled at each dose level after that dose is determined tolerable.

↓

Part 2
Molecularly-Defined Tumor Histology Groups
To determine safety and preliminary evidence of clinical benefit of GSK2849330, and to further evaluate the PK and PD of GSK2849330 at the recommended Part 2 dose(s) and regimen(s) in subjects with selected HER3 or HER3 and NRG1 expressing tumor types.

3.2. Pre-Screening

Subjects will be required to undergo pre-screening to determine if their tumor is HER3 expressing or HER3 and NRG1 expressing (details regarding HER3 and NRG1 expression requirements will be described in the SPM). Subjects with study eligible advanced solid tumors will sign a separate Informed Consent Form (ICF) to allow for pre-screening of archival tumor or tissue from fresh tumor biopsies (obtained using a procedure that is safe for the subject) for HER3 expression by IHC, or for HER3 expression by IHC and NRG1 expression by quantitative real-time polymerase chain reaction (qRT-PCR) assay.

3.3. Part 1: Dose-Escalation Phase

Accelerated dose titration will be used based upon the favorable pre-clinical safety and clinical experience to date with other HER3-targeted therapies (see Section 1.3 and Section 3.6.3). A single subject in Cohort 1 will receive a dose of 1.4 mg/kg weekly, in order to obtain PK samples at defined intervals to guide the dose regimen(s) for subsequent cohorts.

The subject in Cohort 1 must complete a full 28 days of dosing, and the safety and PK data will be reviewed prior to starting Cohort 2. If the first subject becomes unevaluable for reasons other than toxicity, another subject will be recruited. Additional subjects may also be enrolled at 1.4 mg/kg weekly as part of the PK/PD cohorts as described below. The dose-escalation decision and rationale will be documented in writing with copies maintained at each study site and in the master study files at GlaxoSmithKline (GSK).

Starting with Cohort 2, the dose escalation will continue using the Neuenschwander-continuous reassessment method (N-CRM) [Neuenschwander, 2008] with 3 subjects in each cohort as described below. After the first subject is dosed in Cohort 2 and in all subsequent cohorts, the second and third subjects will not be dosed until the first subject has been observed for at least 24 hours for evidence of unanticipated acute toxicity.

Neuenschwander-Continuous Reassessment Method (N-CRM) in Dose Escalation

The decision regarding escalation to the next dose levels of GSK2849330 will be guided by a Bayesian adaptive method called N-CRM. N-CRM is an alternative to the traditional 3+3 design. It is a modified version of the original Continual Reassessment Method (CRM) proposed by [O'Quigley, 1990]. The traditional 3+3 design only uses the safety information from the current dose and ignores the information from previous cohorts. In contrast, the N-CRM model incorporates information from all previous subjects and dose levels as the study progresses, resulting in a more accurate and reliable prediction of dose effects on the future subjects. In this case the 3+3 design and N-CRM collect the same safety information (occurrence of a DLT), but utilize different decision making processes to support dose escalation decisions.

The N-CRM method assumes that the probability of experiencing a DLT is related to dose according to a logistic regression model. The model actively seeks a dose level that produces a pre-specified probability of a DLT occurring by using safety data from all

enrolled subjects to compute a more precise dose-toxicity curve. The model is carried out using Bayesian methods, which requires an initial estimation of prior distribution which characterizes the shape of the dose-toxicity curve. In this case, a weakly informative prior was selected based on clinical experience reported to date for anti-HER3 mAbs (which have not been associated with reported DLTs) and the nonclinical safety data for GSK2849330.

As the study progresses, the absence or presence of DLTs in subjects enrolled at each dose level provides additional information for the model and results in an adjustment of the estimation of distribution to characterize the shape of the dose-toxicity curve (also called posterior distribution). The posterior distribution is then evaluated to identify the dose closest to the acceptable toxicity interval, which is pre-specified as the interval from 16% - 33% DLT rate. This range was selected as the equivalent of between a 1 out of 6 and 1 out of 3 (or 2 out of 6) toxicity rate which guides the traditional 3+3 dose escalation decision.

Implementation of N-CRM: The N-CRM model implementation will be performed using Fixed and Adaptive Clinical Trial Simulator (FACTS) (Version 2.3 or higher) from Tessella.

Bayesian Prior

The N-CRM methodology requires that a Bayesian prior for the toxicity curve be pre-specified. The Bayesian prior used for this design was determined using the quantile method. For each dose, an estimate of the median probability of DLT was specified, along with a 95% credible interval. The 95% credible intervals are intentionally wide due to limited information about the toxicity profile of GSK2849330 in humans. Table 1 shows the median prior probability of experiencing a DLT at the given cumulative dose along with a 95% credible interval around the median:

Table 1 Table of Specified Prior Probability of DLT (with 95% Credible Interval)

Anticipated Dose (mg/kg)	2.5% Quantile for Probability of DLT	Median for Probability of DLT	97.5% Quantile for Probability of DLT
1.4	0.0009739	0.00415	0.5
3	0.002085	0.00851	0.6
10	0.006915	0.02891	0.7
30	0.02046	0.08198	0.8

The 2.5% quantile and median of the prior distribution are based on Roche RGA7116 study human safety data [Meulendijks, 2013] conservatively treating AEs that resulted in discontinuation as if they were DLTs. The 97.5% quantile of the prior distribution is increased by empirical adjustment to weaken the prior by inflation of variance.

Dose recommendation: Dose recommendation output from the N-CRM model will be based on the posterior probabilities that the DLT rate for each escalation dose lies in one of the following categories:

- [0%,16%) range of minimal toxicity
- [16%, 33%) range of acceptable toxicity
- [33%, 60%) range of excessive toxicity
- [60%, 100%) range of unacceptable toxicity

After each cohort, a recommendation will be made to either: 1) escalate to the next dose or regimen, 2) de-escalate, 3) recruit more subjects at the current dose, or 4) stop. The recommended dose will be the one with the highest probability of having a DLT rate in the acceptable toxicity range [16%, 33%), subject to the constraint that no dose may be skipped during dose escalation. The recommended dose has an additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range must be less than 25%. Additional subjects may also be enrolled at any specified dose level to further characterize the safety, as with traditional dose-escalation methods.

Prior to dose escalation/de-escalation, a meeting will be convened to discuss available safety, and the recommendation from the N-CRM model. The data will be reviewed by the investigator(s) and GSK study team which may include the Medical Monitor, statistician, and pharmacokineticist. The dose escalation rationale and decision for the subsequent cohort will be documented in writing with copies maintained at each site and in the GSK study files.

The initial dose levels to be evaluated are outlined in Section 3.6.3.

Additional subjects may also be enrolled at any specified dose level to further characterize safety. Additional doses and schedules and loading doses may be explored, following the rules outlined for dose escalation, based on emerging safety, PK, and PD data.

PK/PD cohort(s): Once a given dose escalation cohort is filled, additional subjects may be enrolled into a PK/PD cohort (at any dose level determined to be tolerable) to allow for the collection of data on the PD effects of GSK2849330 as well as additional PK data.

Subjects enrolled in the PK/PD cohorts must meet all of the relevant inclusion and exclusion criteria, have disease that is amenable to biopsy, and also agree to have pre- and on-treatment biopsies (using a procedure that is safe for the subject) in addition to the other study procedures. Subjects will be enrolled in PK/PD cohorts in order to obtain evaluable pre- and on-treatment biopsy pairs per dose level (see SPM for additional details). Subjects who do not agree to, or who are unable to safely provide pre- and on-treatment biopsies in the PD expansion may be enrolled in dose escalation cohorts in Part 1 as they become available.

Subjects enrolled in the PK/PD cohorts may have their dose escalated to a higher completed dose level (not exceeding the MTD) once the necessary PK/PD procedures have been completed and once other criteria for intra-subject dose-escalation have been met (see Section 3.5). See the PK/PD cohorts Time and Events (Table 9, Table 10) for study assessments specific to the PK/PD cohorts.

The final recommended Part 2 dose regimen(s) will be based on an overall assessment of safety taking into consideration all available data including PK, PD, and the recommendation from the N-CRM model.

3.3.1. Dose-Limiting Toxicity

An event will be considered a DLT if it occurs within the first 4 weeks (28 days) of treatment, and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment:

a. Grade 3 or greater non-hematologic toxicity as described in Common National Cancer Institute-Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [NCI, 2009] that cannot be controlled with routine supportive measures (e.g., antiemetics, antidiarrheals, antihistamines).

b. Grade 4 neutropenia lasting >5 days.

c. Febrile neutropenia, of any grade or duration as defined by NCI-CTCAE version 4.0 [NCI, 2009].

d. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with bleeding.

e. Alanine aminotransferase (ALT) >3x upper limit of normal (ULN) with bilirubin >2x ULN.

f. Any Grade 2 or greater NCI-CTACAE version 4.0 [NCI, 2009] toxicity that in the judgment of the investigator and GSK Medical Monitor, would be considered dose-limiting.

g. Grade 3 or greater decrease in left ventricular ejection fraction (LVEF).

3.3.2. Maximum Tolerated Dose

In the context of the N-CRM approach as described in Section 3.3, the MTD is defined as the dose with the highest posterior probability of subjects experiencing a DLT, in the first 28 days on treatment in the target interval [16%, 33%]. These probabilities 16% and 33% were chosen to be consistent with the traditional 3+3 design toxicity boundary which is 1/6 and 1/3.

Additional dosing schedules with lower dose intensity may be explored as long as they do not exceed the MTD.

3.4. Part 2: Molecularly-Defined Tumor Histology Groups

Part 2 can begin once the recommended dose and schedule is identified in Part 1. It is possible that more than one dose and/or schedule will be evaluated in Part 2 if available PK, PD and safety data suggest that multiple doses and schedules have desirable biologic activity or if an MTD cannot be established.

The selected dose level(s) will be evaluated in Part 2 for confirmation of safety and tolerability, as well as preliminary assessment of clinical benefit, in at least 4 molecularly-defined tumor histology groups of subjects with HER3 or HER3 and NRG1 expressing tumors Group 1 will include subjects with HER3- expressing melanoma. Group 2 will include subjects with HER3-expressing gastric cancer. Group 3 will include subjects with HER3 expressing and NRG1-expressing cancers of the head and neck. Group 4 will include subjects with HER3 expressing and NRG1-expressing NSCLC. All subjects must have archival tissue available for HER3 and if required NRG1 testing or be willing to undergo a tumor biopsy using a procedure that is safe for the subject, to provide a sample for testing.

Each group will initially enroll 12 subjects with the option of expanding to a maximum of 30 subjects if futility criteria are not met using well established methodology of [Lee, 2008] (See Section 13.2.2 and Section 13.6.2 for additional details).

Subjects will be required to have disease amenable to biopsy and agree to pre-and on-treatment tumor biopsies, using a procedure that is safe for the subject. Pre-and on-treatment biopsies are mandatory for all subjects in all groups. GSK will closely monitor and evaluate the collection of evaluable biopsies and will notify the participating centers of any change to the collection requirements for any or all groups.

3.5. Intra-subject Dose-Escalation

A subject's dose level may be increased up to the highest dose level that has previously been confirmed by the investigator and GSK medical monitor as not exceeding the MTD. Intra-subject dose escalations will be allowed in both Part 1 and Part 2 (if multiple doses/regimens demonstrate a better PK profile or clinical activity) provided that the subject has completed at minimum, the first 28 days of treatment with no sign or evidence of disease progression, no toxicity greater than Grade 2 or the occurrence of significant AEs, and prior approval has been obtained from a GSK medical monitor. Subjects will be permitted to increase dose levels multiple times provided the above criteria are met. Any dose escalations must be agreed upon by the investigator and GSK medical monitor, and must be documented on an Intra-subject Dose Escalation Request Form (see the SPM) with copies maintained at the site and in the study files.

3.6. Rationale

3.6.1. Rationale for Study

HER3 expression is seen across a wide variety of solid malignancies and is associated with poor prognosis. Up-regulation of HER3 expression and activity is also associated

with resistance to multiple pathway inhibitors. GSK2849330, a monoclonal antibody targeting HER3, is a new agent for subjects whose tumors express HER3 and/or its ligand, NRG1. GSK2849330 has a unique pharmacologic profile compared to other HER3 antibodies with multiple modes of action including inhibition of tumor signaling and increased potential for direct cell killing via enhanced ADCC and CDC activities. (See Section 1.2.1 for details).

There is considerable unmet medical need across these tumor types where high HER3 expression is seen. The purpose of the dose escalation is to evaluate safety, PK, and initial PD of the drug in subjects with HER3 expressing tumors. Following dose escalation in Part 1, at least 4 molecularly-defined tumor histology groups will be enrolled in Part 2. Preliminary clinical activity, biomarkers of target engagement, downstream signalling, ADCC, and CDC will be evaluated.

3.6.2. Rationale for Population

Subjects will be selected on the basis of HER3 expression on the cell membrane of the tumor because higher levels of target expression on the cell surface is required for ADCC, CDC and signaling inhibition functions of the antibody. High HER3 expression has been demonstrated in the tumor histologies being considered for this trial [Ocana, 2013].

Study eligibility for Part 1 is based on HER3 protein expression using an analytically validated IHC assay. For some groups in Part 2, study eligibility is further defined by NRG1 expression.

HER3 is expressed in a broad range of solid tumors, including melanoma, gastric cancer, NSCLC, and squamous cell carcinoma of the head and neck (SCCHN). Upon ligand binding, HER3 heterodimerizes with other members of the HER family and acts as a mediator of drug resistance to various cancer therapies [Amin, 2010; Zhang, 2014; Kugel, 2014]. Phosphorylation of intracellular sites of HER3 leads to activation of PI3K/AKT and MEK/MAPK and JAK/STAT signaling. GSK2849330 has demonstrated inhibition of HER3 activity and tumor growth in mouse xenograft models.

For Part 2 of the study, 4 tumor types were selected for inclusion: 2 tumor types with high levels of HER3 expression (melanoma and gastric cancer) and 2 tumor types with high levels of NRG1 (ligand for HER3) expression (cancers of the head and neck and NSCLC).

Melanoma

In melanoma, overexpression of HER3 is associated with advanced disease and decreased survival [Reschke, 2008; Ueno, 2008]. Treatment of melanoma is underexplored in the development of HER3 inhibitors.

In CHL-1, BRAF wild-type melanoma cell line mouse xenograft model GSK2849330 treatment decreased phospho-HER3, total HER3, phospho-AKT and tumor growth.

HER3 inhibition restored the sensitivity of trametinib and dabrafenib (MEK and BRAF inhibitors, respectively) in NRG1-treated BRAF mutant melanoma cell lines.

Gastric cancer

Both HER2 and HER3 expression are probable prognostic markers in patients with gastric cancer [Park, 2006; García, 2003; Piontek, 1993; Hayashi, 2008; Zhang, 2009; Wu, 2014; Sato, 2013].

Approximately 30% to 60% of gastric cancers express HER3 [Hayashi, 2008]. HER3 mutations are present in approximately 11% of gastric cancers. In a gastric cancer xenograft model, HER3 antibodies reported to reduce tumor growths. In NCI-N87, an ERBB2 amplified gastric cancer cell line, GSK2849330 treatment restored sensitivity to lapatinib lost due to the addition of NRG1.

Cancers of the Head and Neck

A subset of head and neck cancer cell lines with sensitivity to lapatinib has elevated expression of NRG1 and activation of HER3 [Wilson, 2011]. High NRG1 expression in these cancers is associated with activation of HER3 and may be used as a predictive biomarker for HER3-targeted therapies [Shames, 2013].

A combination of EGFR and HER3 inhibition caused tumor regression in head and neck xenograft models [Zhang, 2014].

NSCLC

NRG1 overexpression was identified as a biomarker for efficacy in patients treated with HER-3 antibody MM-121 [Sequist, 2014]. In a phase 2 trial of patritumab, a HER3-targeted antibody, in combination with erlotinib, an EGFR inhibitor, in erlotinib-naive patients with advanced NSCLC, PFS was significantly improved only in the subgroup of patients with high NRG1 expression [Mendell-Harary, 2014;Von Pawel, 2014]. Furthermore, one PR was confirmed in a patient with NSCLC who expressed high levels of NRG1 in a phase 1 study of HER3 antibody AV-203 that included subjects with advanced or metastatic colorectal cancer, NSCLC, and SCCHN, and other solid tumors [Sarantopoulos, 2014]. Recently, NRG1 gene fusion has been reported in a subset of invasive mucinous lung adenocarcinoma.

Nonclinical data also demonstrated NRG1 induced activation of HER3 signalling adversely affect the activity of agents that target the MEK/MAPK and PI3K/AKT signalling pathways. In KRAS mutant NSCLC cell lines, the combined inhibition of MEK and HER3 synergistically induced cell death. HER3 is upregulated in response to AKT inhibition in some NSCLC cell lines. In vitro studies of patritumab showed that only cell lines expressing NRG1 responded to treatment, as manifested by decreases in HER3 and AKT phosphorylation [Schneider, 2014].

3.6.3. Rationale for Dose

The proposed doses of GSK2849330 are based on available preclinical biology, toxicology, and PK data as well as predicted PK and pharmacologic response information for humans and are consistent with International Conference on Harmonisation (ICH) guidelines for FTIH oncology studies. Guidance for first in human studies with biologics, expert viewpoints on FTIH oncology studies with molecularly targeted therapeutics [LeTourneau, 2010], and recent preliminary safety data reported for anti-HER3 mAbs were also considered when proposing doses of GSK2849330 (refer to Section 1.3 for details).

In nonclinical GLP toxicology studies, GSK2849330 was given as a once-weekly IV infusion to rats and cynomolgus monkeys for up to 4 weeks with up to 6-week off-treatment period. In the rat, there were no adverse findings up to and including the top dose studied (500 mg/kg/wk). In monkeys, abnormal fecal consistency was observed in male animals at the top dose studied (300 mg/kg/wk) and in female animals at ≥ 30 mg/kg/wk. In a single monkey in the top dose group (300 mg/kg/wk), mild cecal and colonic ulcers were observed at terminal necropsy. The NOAEL, STD10 (severely toxic dose in 10% of animals [rat], and HNSTD (highest non-severely toxic dose [cynomologus moneky]), and HED (human equivalent dose) corresponding to the STD10 or NHSTD are summarized in Table 2.

Table 2 NOAEL, NSTD10 (rat), and HNSTD (primate) from GLP Toxicology Studies and HED Predictions[a]

	NOAEL Dose (mg/kg/wk)	NOAEL AUC (0-168 h) (mg*hr/mL)	STD10 or HNSTD Dose (mg/kg/wk)	Human Equivalent Dose (mg/kg/wk)
Rat	500	573	≥500	≥81
Cyno	30	102	≥300	≥97

AUC = area under the concentration-time curve; Cyno = cynomolgus monkey; HED = human equiv. dose HNSTD = highest non-severely toxic dose; NOAEL = no observed adverse effect level; STD10 = severely toxic dose in 10% of animals.

a. HED corresponding to the STD10 (rat) or HNSTD (Cyno) as calculated scaled using scaling factor described in the FDA FTIH guidance

Refer to Section 1.2 and the IB [GlaxoSmithKline Document number 2013N168399_01] for additional information on the preclinical biology and toxicology studies.

Starting Dose

The proposed starting dose is 1.4 mg/kg, administered once-weekly. According to ICHS9 guidance, calculating a starting dose based on HNSTD/6 in the most relevant species (cynomologous monkey) yields a starting dose of ~16 mg/kg/wk. We selected a more conservative starting dose of 1.4 mg/kg/wk, slightly above the MABEL calculated from tumor xenograft studies, which in turn suggests that clinical activity may be observed at dose levels of 1.2 mg/kg and higher.

Table 3 Dose Levels

Cohort	Dose	N Dose Escalation Cohorts	N PK-PD Cohorts
1	1.4 mg/kg weekly	1 (minimum)	up to 3
2	3 mg/kg every 2 weeks	3 (minimum)	up to 3
3	10 mg/kg every 2 weeks	3 (minimum)	up to 3
4	30 mg/kg every 2 weeks	3 (minimum)	up to 3
5	30 mg/kg weekly (optional change to every 2 weeks after 24 weeks of treatment)	3 (minimum)	up to 3
Additional optional cohorts may be enrolled at different dose levels and intensities			

Maximum Proposed Dose

The maximum proposed dose of 30 mg/kg for weekly, bi-weekly or every three week dosing was selected based on PK-PD extrapolations which predict target engagement > 90% and tumor saturation should be achieved at or below this dose, and based on practical considerations (e.g., drug product supply and production capacity) Emerging PK, safety and tolerability data may cause the proposed maximum dose to be adjusted downward (see Section 3.3 for details of the N-CRM model assessment of safety data).

Dose Escalation

The proposed dose escalation scheme is based on a half-log step size, with the exception of the 30 mg/kg/wk dose and the nominal doses shown in Table 3 represent the maximum dose which may be selected. The study team, in discussion with the investigator(s), may select other doses or alternative schedules besides those shown, based on emerging safety, tolerability, PK and/or PD data.

Dosing Interval

The predicted half-life for GSK2849330 after the first dose is ~7 days and increases to ~10 to 14 days after repeated dosing and is expected to support dosingfrequency from weekly to every three weeks. However, at lower doses, including the proposed starting dose, the contribution of target mediated clearance may yield a half-life somewhat shorter than projected for higher dose levels. With this consideration, the initial dosing frequency for the first subject will be once-weekly. PK data will be evaluated from the first week of dosing for the first subject, so that adjustments in the dosing interval can be made if appropriate (see the Time and Events Tables Section 7.1 and Section 7.4 for the specific PK assessment schedule for the first subject).

If the half-life appears to be generally in line with expectations, the dosing interval for higher dose cohorts is anticipated to be every week or every 2 weeks. A general guideline is shown in Table 4. Additional schedules may be explored based on safety, tolerability, PK and PD.

Table 4 Dosing Interval Guidance

Observed half-life	Likely dose interval*
<3 days	Once-weekly
4-8 days	Every week or every 2weeks
> 9 days	Every 3 weeks

*Final selection of dose interval for cohorts will take into consideration the half-life together with safety, tolerability, PK and available PD data.

It is recognized that increasing the dose can allow for extension of the dosing interval with equivalent safety and efficacy, assuming that 1) toxicity is not limited by Cmax and 2) efficacy is related to overall exposure (AUC) or time above a given concentration. Both assumptions appear reasonable for GSK2849330 based on 1) preclinical safety data and 2) preclinical efficacy data and knowledge of the mechanism of action. Based on human PK predictions from cynomolgus monkey data, a dose of 2.9 mg/kg every 3 weeks IV may provide the same exposure in 3 weeks as 3 doses of 1.2mg/kg every week IV at steady state. Using these principles, it is anticipated that the dosing schedule may be lengthened as appropriate based on accrual of PK and/or PD information.

Additional context for the proposed doses are provided in the following sections.

Human Pharmacokinetic Extrapolation

Human plasma PK was predicted based on extrapolation from PK data of GSK2849330 in cynomolgus monkeys dosed with 1, 10 or 100 mg/kg as a single IV dose (n= 3 female and n= 3 male per group). The estimated terminal half-life from the high dose (100 mg/kg) in a 3-kg cynomolgus monkey was 100-114 hours with central volume of distribution of 140 mL (8% coefficient of variance [CV]) and target mediated clearance equilibrium constant 7.2 µg/mL (57% CV). Single species allometric scaling from 3 kg cynomolgus monkey to a 60 kg human predicts a terminal half-life in humans of approximately 197-224 hours (~8-9 days) with central volume of distribution approximately 2.9 L and equilibrium constant approximately 3.7 µg/mL (57% CV), assuming the same level of target in cynomolgus and human.

Preliminary Human Pharmacokinetic Profile

Arithmetic mean preliminary non-compartmental PK parameters as of September 2014 are listed in Table 5 below for dose-escalation cohorts in this trial dosed GSK2849330 at 1.4 mg/kg, 3 mg/kg or, 10 mg/kg.

Table 5 Preliminary non-compartmental Pharmacokinetic Profile

Parameter	Unit	n	Treatment (mg/kg)	Estimate (CV%)
AUC(0,336)	h*µg/mL	1	1.4	3123
		3	3	8880 (25.7)
		3	10	28100 (27.8)
$t_{1/2}$ (24, 168)	hr	1/3	1.4	78.7
$t_{1/2}$ (24, 336)	hr	1/3	3	119
		3	10	134 (32.0)
C_{max}	µg/mL	1	1.4	29.8
		3	3	64.7 (30.2)
		3	10	234 (2.65)
t_{max}	hr	1	1.4	1
		3	3	1 [1-6][a]
		3	10	1[1-6] [a]

AUC = area under the concentration-time curve; Cmax = maximum observed concentration; CV = coefficient of variance; t1/2 = plasma elimination half-life; tmax = time to maximum observed concentration.
Preliminary non-compartmental PK analysis for subjects in dose-escalation cohorts.
a denotes median [range]

Preliminary population PK parameters based on nominal dose and PK sample time as of September 2014 are listed in Table 6 below for dose-escalation cohorts at 1.4 mg/kg (n=1), 3 mg/kg (n=2) or, 10 mg/kg (n=2). The data are modelled according to a two compartment PK model with peripheral Target Mediated Drug Disposition. The value of KM (concentration at half maximal saturation of peripheral target mediated drug disposition) is based on Biacore *in vitro* binding data together with an assumed 4/h rate of internalization and degradation based on semi-quantitative *in vitro* pulse chase experiment. One subject was excluded from the 3 mg/kg cohort because the dose was delayed; and another subject was excluded from the 10 mg/kg cohort because the infusion was terminated early so the total dose of GSK849330 administered was uncertain.

Table 6 Preliminary Population PK Parameters

Parameter	Unit	Estimate	%RSE	%CV
CL	mL/h	11.4	39.1	31.3
V1	mL	2830	6.64	
VM	µg/h	198	40.6	
KM	µg/mL	0.513		
Q	mL/h	79.0	19.1	
V2	mL	3420	13.7	
D1	h	1		
SG1 (proportional)		0.0626	62.9	

The compartmental and non-compartmental model parameters suggest a catabolic half-life of (V1/CL)xln(2) = 172 hours.

Predicted Effective Dose

The potential therapeutic dose range for GSK2849330 in humans was derived using available preclinical *in vitro* and *in vivo* PK and efficacy data. In addition, data from mouse *in vivo* CHL-1 xenograft efficacy studies were evaluated to predict the potential minimum clinically efficacious dose. PK/PD modeling of CHL-1 xenograft data in SCID mice suggests that anti-tumor efficacy (based on tumor growth curves) may be achieved with systemic plasma trough concentrations of GSK2849330 maintained at ≥ 20 µg/mL. The predicted human equivalent dose to achieve a similar trough concentration in 90% of the population is approximately 1.4-3 mg/kg/wk. This dose is also in line with that projected, based on *in vitro* potency data, to engage HER3 and inhibit signaling (approximately 0.9 to 5.6 mg/kg). It is anticipated that optimal anti-tumor activity will require full target engagement and that ADCC and CDC enhancements may further increase the anti-tumor activity of GSK2849330. However, it is also recognized that saturation of target throughout the tumor in the clinical setting may require doses higher than those projected based on preclinical extrapolations, due to factors in the tumor microenvironment such as vascular perfusion heterogeneity which may limit mAb intra-tumoral distribution. Recognizing these factors, the top proposed dose for evaluation is 30 mg/kg, a dose which is also viewed as the highest dose feasible based on practical considerations.

A loading dose scenario is predicted to maintain an accumulated steady state trough concentration if the dosing interval is less than or equal to the elimination half-life. Accordingly, a 30 mg/kg weekly IV dose cohort has been added to the dose escalation portion of the study.

3.6.4. Rationale for Endpoints

The safety endpoints for all parts of the study (as described in Section 2.1 and Section 2.2) are designed to maximize subject safety, to allow for the identification and monitoring of emerging safety signals, and to allow for the identification of DLTs for determination of a MTD and/or recommended dose for further exploration.

Efficacy endpoints (as described in Section 2.1 and Section 2.2) will be collected to evaluate preliminary evidence of clinical benefit from treatment with GSK2849330.

Non-compartmental PK parameter values for GSK2849330 following IV administration, including area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments [AUC(0-t)], Area under the concentration-time curve over the dosing interval [AUC(0-τ)], Cmax and time of occurrence of Cmax (tmax) and mean residence time (MRT) of GSK2849330 together with population compartmental PK parameters including clearance (CL), systemic volume of distribution (V), distributional clearance (Q), maximal rate (Vm), and concentration at half maximal rate (Km) according to a Michaelis-Menten approximation of systemic target mediated clearance [Gibiansky, 2008], were selected to characterize the PK activity of GSK2849330.

Tumor, skin, and circulating biomarkers were selected based on the mechanism of action of GSK2849330, preclinical evidence in addition to clinical evidence reported in agents of the same class and in those affecting similar pathways. The objective is to characterize the PD effect of GSK2849330 and to obtain preliminary data on the relationship between HER3 expression levels (e.g., IHC 2+ and 3+), NRG1 expression, other potential predictive biomarkers including expression of other RTKs, mutations, immune associated markers, and efficacy outcome.

3.7. Study Treatment

3.7.1. Treatment Assignment

- Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

- Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the GSK interactive voice response system (IVRS) by the investigator or authorized site staff. All enrolled subjects will receive GSK2849330.

3.7.2. Dosage and Administration of Study Treatment(s)

GSK2849330 will be given by IV infusion over a 1-hour period. If an infusion-related reaction occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator and/or GSK medical monitor, depending on the severity of the symptoms; the subject will receive appropriate medical treatment. When the subject's condition is stable, the infusion may be restarted according to the judgment of the investigator. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused.

Guidance for the monitoring and managing of infusion related reactions and allergic/hypersensitivity reactions, including anaphylaxis, are outlined in Section 3.9.1 and Section 3.9.2.

Subjects should be monitored for at least 1 hour after the completion of the infusion and may be discharged if considered clinically stable and all other study procedures have been completed.

Guidelines for dosage modifications are provided in Section 3.9.4.

The dose of study treatment is discussed in Section 3.3 and Section 3.4.

3.7.3. Blinding

This is an open-label study.

3.8. Safety Management Guidelines

3.8.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold stopping criteria have been designed to assure subject safety and to evaluate liver event etiology during administration of study treatment(s) and the follow-up period. Study treatment(s) will be stopped if any of the following liver chemistry stopping criteria is/are met:

1. ALT ≥3 times ULN and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and international normalization ratio [INR] >1.5)

NOTE: Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).

2. ALT ≥5 times ULN.
3. ALT ≥3 times ULN if associated with the appearance or worsening of rash or hepatitis symptoms (fatigue, nausea, vomiting, right upper quadrant pain, tenderness or jaundice) or hypersensitivity (such as fever, rash or eosinophilia, other than that as described in Section 3.9.1 and Section 3.9.2).

4. ALT ≥3 times ULN persists for ≥4 weeks.
5. ALT ≥3 times ULN and cannot be monitored weekly for 4 weeks.

Subjects with ALT ≥3 times ULN **and** <5 times ULN **and** bilirubin <2 times ULN, who do not exhibit hepatitis symptoms or rash, can continue study treatment(s) as long as they can be monitored weekly for 4 weeks. See following section for details on weekly follow-up procedures for these subjects.

3.8.1.1. Liver Chemistry Follow-up Procedures

Refer to the diagram in Appendix 1 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 3.8.1.

- Immediately and permanently withdraw the subject from study treatment.
- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment(s) cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event electronic case report forms (eCRFs). If the event also meets the criteria of a SAE (see Section 8.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study and do not rechallenge with study treatment(s).

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN:

- Monitor subjects **weekly** until liver chemistries (ALT, aspartate aminotransferase [AST], alkaline phosphatase [ALP], and bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3 times ULN and bilirubin ≥2 times ULN (or ALT ≥3 times ULN and INR >1.5):

- **This event is considered an SAE** (see Section 8.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects **twice weekly** until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

In addition, for <u>all</u> subjects with ALT ≥3 times ULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - Hepatitis A Immunoglobulin M (IgM) antibody.
  - Hepatitis B surface antigen and hepatitis B core antibody (IgM).
  - Hepatitis C RNA.
  - Cytomegalovirus IgM antibody.
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
  - Hepatitis E IgM antibody (if subject resides outside the United States (US) or Canada, or has traveled outside US or Canada in past 3 months).
- Blood sample for PK analysis, obtained within 30 days of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment(s) prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated <u>OR</u> a PK sample cannot be collected in the time period indicated above, **do not obtain a PK sample**. Instructions for sample handling and shipping are included in the SPM.
- Serum creatine phosphokinase and lactate dehydrogenase.
- Fractionate bilirubin, if total bilirubin ≥2 times ULN.
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (other than as described in Section 3.9.1 and Section 3.9.2) such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia, on the AE eCRF.
- Record use of concomitant medication(s), acetaminophen, herbal remedies, other over-the-counter medication(s), or putative hepatotoxins on the Concomitant Medications eCRF.
- Record alcohol use on the Liver Events eCRF.

The following are required for subjects with ALT ≥3 times ULN **and** bilirubin ≥2 times ULN but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, magnetic resonance imaging [MRI] or computed tomography [CT] scan) to evaluate liver disease.
- Liver Imaging and/or Liver Biopsy eCRFs are also to be completed if these tests are performed.

- Serum acetaminophen adduct high-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]).

3.8.2. QTc Stopping Criteria

If a subject meets the QTc[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval corrected for heart rate (HR) by Fredericia's formula (QTcF) >530 msec

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (e.g., within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should have study treatment(s) withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment(s) if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

Refer to Appendix 2 for country-specific QTc stopping criteria.

3.8.3. Left Ventricular Ejection Fraction (LVEF) Stopping Criteria

3.8.3.1. LVEF Stopping Criteria

Echocardiography (ECHO) or multi gated acquisition scan (MUGA) must be performed at Screening and as outlined in the Time and Events Tables (Section 7.1). Subjects who have an asymptomatic, absolute decrease of >15% in LVEF compared with baseline or an absolute decrease of >10% in LVEF compared with baseline and the ejection fraction is below 50% should temporarily discontinue GSK2849330 and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1 to 2 weeks for 4 weeks or until LVEF recovery to within15% of baseline or to above 50% and within 10% of baseline depending on which stopping criteria above were met.

- If the LVEF recovers (defined as absolute decrease ≤15% compared to baseline or ≥50% and absolute decrease ≤10% compared with baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK2849330 at a reduced dose. For such subjects, monitoring of LVEF will be performed 2, 4, and 8 weeks after rechallenge, and then per protocol.
- If repeat LVEF does not recover within 4 weeks, treatment with GSK2849330 should be permanently discontinued. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution.

Subjects with Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue treatment with GSK2849330. Ejection fraction should be monitored every 4 weeks for a total of 16 weeks or until resolution. If recovery occurs (LVEF ≥50% and

symptom resolution) within 4 weeks, treatment with GSK2849330 may be restarted at a reduced dose if the subject is receiving clinical benefit and in consultation with the GSK Medical Monitor.

Copies of all ECHOs/MUGAs and cardiology consultations performed on subjects who experience a >15% decrease in LVEF from baseline or >10% decrease in LVEF from baseline and whose cardiac ejection fraction is < 50% will be required by GSK for review. Instructions for submitting qualifying ECHOs are provided in the SPM.

3.9. Guidelines for Events of Special Interest and Dose Modifications

The severity of AEs will be graded utilizing NCI-CTCAE, version 4.0 [NCI, 2009]. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section.

In subjects experiencing suspected infusion-related reactions, a whole blood sample for selected cytokines (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours and submitted to the central laboratory for analysis (see SPM for instructions).

3.9.1. Management of Infusion Reactions

As there is a risk of infusion reactions during administration of IV immunoglobulins, including monoclonal antibodies, subjects will be monitored for signs and symptoms of an infusion-related reaction (including Grade 1 to 2 fever, chills, headache, nausea, malaise) during infusion and for a minimum of 1 hour after the first administration of GSK2849330.

If an infusion-related reaction occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator and/or GSK medical monitor, depending on the severity of the symptoms and the subject will receive appropriate medical treatment. For subsequent infusions, the investigator may provide premedication with antihistamines, acetaminophen, and/or corticosteroids and may reduce the starting infusion rate.

Treatment may include:

- **Fevers/Myalgia:** Initiate treatment with acetaminophen (paracetamol). If subject's fever does not respond to acetaminophen, consideration should be given to the use of a nonsteroidal anti-inflammatory drug (NSAID) such as indomethacin. Consider pre-medication with acetaminophen for subsequent doses.
- **Chills/rigors:** Use warming blankets as initial intervention; consider IV meperidine (pethidine) if chills persist.
- **Nausea/vomiting:** Consider treatment with 5-HT3 antagonists, prochlorperazine, lorazepam; some agents may cause hypotension and altered mental status; therefore, these agents should be used with caution.

3.9.2. Allergic Reaction Monitoring and Management

As GSK2849330 is a fully humanized antibody, it is considered unlikely for acute allergic reactions to occur in response to GSK2849330 exposure; however, all subjects will be monitored carefully for evidence of allergic response. A subject that exhibits signs or symptoms of severe hypersensitivity or anaphylaxis will receive appropriate medical treatment and remain on study at the discretion of the investigator and after discussion with the GSK medical monitor.

In accordance with the preparedness for treatment of anaphylaxis, emergency resuscitation equipment, advanced cardiac life support equipment, and medications must be readily accessible during GSK2849330 administration.

It is important to recognize early signs of an anaphylaxis reaction and appropriate treatment must begin immediately to prevent progression to severe anaphylaxis. Subjects will be closely monitored in an appropriate setting for early signs of dyspnea and edema. Antihistamines, such as diphenhydramine; and corticosteroids such as prednisolone may be given to reduce symptoms.

If more severe clinical signs arise, immediate assessment of the ABC's (airway, breathing, and circulation from Basic Life Support) will be done in all suspected anaphylactic reactions. Cardio-Pulmonary Resuscitation (CPR) will be initiated if needed. Epinephrine will be given by injection without delay. Emergency interventions may include endotracheal intubation or tracheostomy. Treatment for shock will include IV fluids and medications that support the actions of the heart and circulatory system.

3.9.3. Diarrhea Management

If episodes of diarrhea occur, causes for the diarrhea other than the study treatment such as concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by *Clostridium. difficile* or other pathogens, partial bowel obstruction, etc., should be ruled out. Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity. Supportive measures depend on the severity of the diarrhea and could include the following as clinically indicated:

- Dietary modifications (e.g. small, frequent meals, low fiber, and lactose-avoidance; addition of foods rich in potassium)
- Maintain hydration with clear liquids or IV fluids as needed
- Loperamide and/or oral antibiotics
- Second-line agents
- Hold GSK2849330

Additional recommended guidelines for the treatment of study treatment induced diarrhea are provided in Benson, et.al. [Benson, 2004] and in Appendix 9.

3.9.4. Dose Modifications

In the event of a toxicity that meets the guidelines for DLT (Section 3.3.1) or is otherwise considered to be clinically significant by the treating physician, treatment will be stopped and supportive therapy administered as clinically indicated. If clinically significant drug-related toxicity is present, treatment should be delayed until the toxicity resolves (with or without supportive therapy) to baseline or ≤Grade 1. If the toxicity does not resolve to ≤Grade 1 or baseline within 2 weeks, withdrawal from the trial is recommended unless otherwise agreed to by a GSK Medical Monitor and the investigator based on evidence of clinical benefit.

For subjects enrolled in the 30 mg/kg weekly dosing cohort, the dosing frequency may be reduced to every 2 weeks at the discretion of the investigator for a toxicity that does not automatically necessitate a dose reduction.

3.9.5. Dose Reductions

Part 1: A subject who experiences a toxicity at any time during treatment with GSK2849330 that either meets the guidelines for DLT (Section 3.3.1) or is otherwise considered to be clinically significant by the treating physician, should have their dose reduced to the previously tested next lower dose level. Any subject who experiences one or more recurrent clinically significant toxicities after the initial dose reduction may have one further dose reduction except where noted otherwise. Subjects who continue to experience clinically significant toxicity despite two dose reductions (i.e., unacceptable toxicity) will be discontinued from the study.

Part 2: Subjects who begin the selected dose and require a dose reduction (due to tolerability/toxicity issues), should be dose reduced to one level below the recommended Part 2 dose. Further dose reductions should be discussed with the GSK Medical Monitor.

4. INVESTIGATIONAL PRODUCT(S)

The term ‘study treatment’ is used throughout the protocol to describe the investigational product (IP) received by the subject as per the protocol design. The study was initiated with vials containing 1 mL of IP. Vials containing 5 mL were later introduced, and for the remainder of the study, both 1-mL and 5-mL vials will be available.

4.1. Description of Investigational Product(s)

Product name :	**GSK2849330 solution for infusion 100 mg/mL**
Formulation description:	Solution containing 100 mg/mL GSK2849330 in vials containing 1 mL for injection or Solution containing 100 mg/mL GSK2849330 in vials containing 5 mL for injection
Dosage form :	Solution for Infusion. The solution is stored at 2-8°C.
Unit dose strength(s)/Dose Level(s):	IV/100 mg/mL (refer to Section 3.3 and Section 3.4 for dose levels)
Physical Description:	GSK2849330 solution for infusion is clear to opalescent, pale yellow or pale brown in color.
Route/ Administration/ Duration:	Delivered as an IV solution (see Section 3.7.2).
Dosing instructions:	Dilute GSK2849330 solution into a 0.9% sodium chloride IV bag to the appropriate concentration for the dose. Deliver the entire contents of the IV bag to the subject.
Manufacturer/ Source of Procurement:	GSK

GSK2849330 will be provided to sites by GSK. The contents of the label will be in accordance with all applicable regulatory requirements.

4.2. Preparation/Handling/Storage of GSK2849330 GSK Investigational Product

Preparation

Dilute GSK2849330 solution into a 0.9% sodium chloride IV bag to the appropriate concentration for the dose. Deliver the entire contents of the IV bag to the subject. The administration kits can be polymerizing vinyl chloride (PVC) or polyolefin (PO) plastics. A 0.22-μM polyethersulfone (PES) filtration set will be used for this study.

Handling

Under normal conditions of handling and administration, IP is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists.

In the case of unintentional occupational exposure notify the study monitor, the GSK Medical Monitor and/or the study manager.

Refer to the SPM for detailed procedures for the disposal and/or return of unused study treatments.

Storage

GSK2849330 must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the GSK2849330 will be limited to the investigator and authorized site staff. GSK2849330 must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

GSK2849330 is to be stored at a temperature range of 2°C to 8°C. Maintenance of a temperature log (manual or automated) is required.

4.3. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of IP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

4.4. Treatment Compliance

GSK2849330 will be administered IV to subjects at the study site. Administration will be documented in the source documents and reported in the eCRF.

Treatment start and stop dates, including dates and reasons for treatment delays and/or dose modifications will also be recorded in the dosing eCRF.

4.5. Treatment of Investigational Product Overdose

In the event of an overdose (defined as administration of more than the highest protocol-specified dose) of GSK2849330, the investigator should:

- contact the GSK Medical Monitor immediately
- closely monitor the subject for AEs/SAEs and laboratory abnormalities for at least 45 days or 5 half-lives (whichever is longer) for GSK2849330
- obtain a plasma sample for PK analysis within 30 days from the date of the last dose of study treatment if requested by the GSK Medical Monitor (determined on a case-by-case basis)
- document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the GSK Medical Monitor based on the clinical evaluation of the subject.

5. STUDY POPULATION

5.1. Number of Subjects

The number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that approximately 13 subjects will be enrolled in Part 1 dose escalation if there are no DLTs observed; if there are any DLTs observed, more than 13 subjects can be enrolled in dose escalation. Up to an additional 21 subjects with evaluable pre- and on-treatment paired biopsies can be enrolled for the purpose of the PK/PD cohorts in Part 1. Therefore, up to approximately 34 subjects may be enrolled into Part 1 (dose-escalation and PK/PD cohorts) of the study; however; additional dose escalation cohorts may be enrolled to allow for further evaluation of additional dose levels/regimens if warranted.

In Part 2 of the study, there will be at least 4 molecularly-defined tumor histology groups. It is estimated that a minimum of 12 subjects will be enrolled in each group with a maximum of approximately 30 subjects if futility criteria are not met. Therefore,approximately120 subjects may be enrolled in Part 2 and approximately 154 subjects may be enrolled in the entire study; however, this number will be considerably fewer if futility conditions are met for any group in Part 2 (see Section 3.4, Section 13.2.2, and Section 13.6.2). Additional groups of tumor histologies predicted to be sensitive to the study drug based on emerging nonclinical or clinical data may be added to Part 2.

In Part 1 (dose escalation) of the study, if subjects prematurely discontinue for reasons other than toxicity, additional subjects may be enrolled as replacement subjects and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the investigator. Subjects may also be replaced in Part 2 of the study for the purpose of testing futility or to facilitate collection of sufficient tumor biopsies for exploratory analyses.

5.2. Subject Selection Criteria

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK study treatment that may impact subject eligibility is provided in the IB.

Deviations from inclusion/exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

5.2.1. Pre-screening Inclusion Criteria for Part 1

Subjects will be eligible for inclusion in pre-screening for the study (See Section 3.2) only if all of the following criteria apply:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. Performance Status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 3).
4. Sufficient archival tumor specimen is available for HER3 IHC analysis, or subject is willing to undergo a fresh tumor biopsy (using a procedure that is safe for the subject) for HER3 IHC analysis (see Section 7.6.1.1 for details).
5. Histologically or cytologically confirmed diagnosis of one of the following solid tumor malignancies for which no standard therapeutic alternatives exist:

    - Bladder cancer
    - Breast cancer
    - Castrate-resistant prostate cancer
    - Cervical cancer
    - Colorectal cancer (CRC)
    - Gastric cancer
    - Hepatocellular carcinoma (HCC)
    - Melanoma
    - Non-small cell lung cancer (NSCLC)
    - Ovarian cancer
    - Pancreatic cancer
    - Squamous cell cancers of the head and neck region (SCCHN) (including parotid and nasopharynx)

5.2.2. Pre-screening for Part 2

Subjects with melanoma, gastric/gastroesophageal cancer, head and neck cancer, or NSCLC who appear to meet all inclusion and exclusion criteria may be pre-screened for the study provided that sufficient tumor specimen, either from archival FFPE tissue or tissue obtained by biopsy (using a procedure that is safe for the subject) is available for analyzing HER3 by IHC or HER3 by IHC and NRG1 by RNA analysis.

5.2.3. Screening Inclusion Criteria for Parts 1 and 2

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. For subjects enrolled in Part 1:subjects must have tumors with documented HER3 expression (2+ or 3+) on the cell surface of the invasive component of the tumor using an analytically validated IHC assay by central laboratory (see Section 7.6.1.1 for details). Subjects enrolled in Part 2 must meet inclusion criterion 9 listed below.

4. ECOG performance status of 0 or 1 (see Appendix 3).

5. Adequate baseline organ function defined by:

SYSTEM	LABORATORY VALUES
Hematologic	
ANC	≥1.5 × 10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥75 × 10^9/L
PT/INR and	≤1.3 × ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 × ULN
AST and ALT	≤2.5 × ULN
Renal	
Serum creatinine OR Estimated glomerular filtration rate or 24-hour urine creatinine clearance[a]	≤ULN OR ≥50 mL/min
Cardiac	
LVEF	≥50% by ECHO[b] or MUGA

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECHO = echocardiogram; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition scan; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

a. Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease (MDRD) equation (Appendix 4). When both a calculated and 24-hour creatinine clearance are available, the 24-hour value will be used.
b. ECHO is the preferred method. MUGA should be performed only if evaluation by ECHO is not available.

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6. If the subject is female, she must be of non-childbearing potential, i.e., have a current tubal ligation, hysterectomy, ovariectomy or be post menopausal, or if she is of childbearing potential, she must have a negative serum pregnancy test within 7 days of first dose of study treatment and agree to use effective contraception, as defined in Section 11.1.1, from the time of the first dose of study treatment until 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.

7. Men with a female partner of childbearing potential must have either had a prior vasectomy or agree to use effective contraception as described in Section 11.1.2 from the time of the first dose of study treatment until 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment to allow for clearance of GSK2849330 in seminal fluid.

8. Subjects enrolled as part of the PK/PD cohort (Part 1) must agree to undergo pre- and on-treatment tumor biopsies, using a procedure that is safe for the subject.

5.2.4. Inclusion Criteria for Part 2 ONLY

As listed above for Part 1, with the exception of criterion 3 which should be replaced with the following criterion 9 and the addition of criteria 10 and 11.

9. For Group 1: subjects with previously treated, unresectable stage III or IV melanoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor using an analytically validated IHC assay by central laboratory.
    - Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with BRAF V600 mutations who already received or were intolerant of prior BRAF inhibitor therapy may be included.
        - Subjects may be included if they had prior immune therapy, or were intolerant of prior immune therapy.

    For Group 2: Subjects with previously treated, unresectable stage III or IV gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor using an analytically validated IHC assay by central laboratory.
    - Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with HER2 positive disease may be included if they had prior anti-HER2 therapy or were intolerant of prior anti-HER2 therapy.

    For Group 3: Subjects with previously treated, unresectable stage III or IV cancers of the head and neck with documented HER3 expression on the cell surface of the tumor (≥1+) and NRG1 expression using analytically validated assays by central laboratory.
    - Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
    - Subjects with locoregional recurrences amenable to definite surgery or additional radiation are excluded.

    For Group 4: Subjects with previously treated, unresectable stage III or IV NSCLC with documented HER3 expression on the cell surface of the tumor (≥1+) and NRG1 expression using analytically validated assays by central laboratory.

    - Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).
    - Subjects with anaplastic lymphoma kinase (ALK) translocation who already received or were intolerant of prior anti-ALK therapy may be included.
    - Subjects with EGFR mutations (e.g., exon 19 deletion and exon 21 L858R) who have documented progression (based on RECIST 1.1) or who were intolerant of prior EGFR inhibitors may be included.

Additional tumor histology groups predicted to be sensitive to the study drug based on biomarkers (e.g., HER3 mutations, NRG translocations) supported by preclinical or clinical data may be added based on emerging data.

10. Subjects must have at least one measurable lesion per RECIST v1.1.
    NOTE: If the only site of measurable disease has been previously irradiated, documented progression of disease and a 4-week interval since completion of radiotherapy is required.

    NOTE: In subjects with >1 measurable lesion, a measurable lesion may be biopsied at Screening and Day 15; however that lesion must not be selected as a target lesion for disease assessment.
11. Subjects must have disease amendable to biopsy and agree to undergo pre- and on-treatment tumor biopsies using a procedure that is safe for the subject (until the participating centers receive written notification from the Sponsor that paired tumor biopsies are no longer required).

5.2.5. Screening Exclusion Criteria for Parts 1 and 2

Subjects meeting any of the following criteria must not be enrolled in the study:

1. Subjects with leptomeningeal or brain metastases or spinal cord compression.
    - Subjects with untreated brain or meningeal metastases are not eligible (computed tomography [CT] scans are not required to rule this out unless there is a clinical suspicion of central nervous system [CNS] disease).
    - Subjects with treated and radiologic or clinical evidence of stable brain metastases (confirmed by 2 scans at least 4 weeks apart), with no evidence of cavitation or hemorrhage in the brain lesion are eligible providing that they are asymptomatic and do not require corticosteroids. Subjects are not permitted to receive enzyme inducing anti-epileptic drugs.
2. Prior HER3- directed treatment (HER2- or EGFR-directed treatment is acceptable).
3. Use of an investigational anti-cancer drug within 28 days (or 5 half-lives, whichever is longer) preceding the first dose of GSK2849330 OR chemotherapy within the last 3 weeks (6 weeks for prior nitrosourea or mitomycin C) OR any major surgery, radiotherapy, immunotherapy or any other anti-cancer therapy within the last 4 weeks, except as noted above.
4. Unresolved toxicity greater than NCI-CTCAE, version 4.0 [NCI, 2009] Grade 1 from previous anti-cancer therapy except alopecia and stable anemia (i.e., untransfused Hb ≥9.0 g/dL without the need for supportive transfusion within 2 weeks of screening) at the time of treatment allocation.

5. Known or suspected hypersensitivity reaction to prior biologic therapy (e.g., therapeutic monoclonal antibody) that in the opinion of the investigator is a contraindication to their participation in the study.

6. Current use of a prohibited medication or requires any of these medications during treatment (Section 10.2).

7. History or evidence of significant cardiovascular risk including any of the following:

   - LVEF <50%
   - A QT interval corrected for HR (QTc) ≥480 msec (≥500 msec for subjects with bundle branch block)
   - History or evidence of current clinically significant uncontrolled arrhythmias.
     Exception: Subjects with controlled atrial fibrillation for >30 days prior to enrollment are eligible.

   - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
   - History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).

8. Known human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which will be allowed).

9. Evidence of another active malignancy (excludes non-melanoma skin cancer). Consult GSK Medical Monitor if unsure whether second malignancies meet requirements specified above.

10. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.

11. Concurrent medical condition that in the investigator's opinion would jeopardize compliance with the protocol.

12. Lactating female.

13. Receiving chronic immunosuppressive therapies (includes daily steroid doses in excess of 20 mg/day of prednisone).

6. COMPLETION OR WITHDRAWAL OF SUBJECTS

6.1. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site and the reason for screen failure will be transmitted to GSK.

6.2. Subject Completion Criteria

In Part 1, a subject will be considered to have completed the study if they complete screening assessments and at least one study treatment followed by at least 28 days of observation. In Part 2, a subject will be considered to have completed the study if they have completed at least one on-treatment disease assessment.

6.3. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.8.1 . In addition, study treatment may be permanently discontinued for any of the following reasons:

- major deviations(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- a dose delay for toxicity of > 2 weeks unless the investigator or GSK Medical Monitor agree that further treatment may benefit the subject
- intercurrent illness that prevents further administration of study treatment
- subject is lost to follow-up, or the study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

If the subject voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Tables (see Section 7.1).

6.4. Study Completion

The study will be considered complete that is, having met the study objectives, after 70% of the subjects have died or 2 years after the last subject is enrolled. Upon completion of the study, if subjects are still continuing to receive benefit from GSK2849330, plans will be developed to provide continued access for those subjects if warranted.

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit (LSLV).

6.5. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given for the post-study care of the subject's medical condition whether or not GSK is providing specific post-study treatment.

7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments being performed. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, ECG, ECHO/MUGA) obtained prior to their signing the informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol and have been performed within the protocol-specified timeframe. However physical exam, medical history, ECOG performance status, and vital signs must be conducted after the informed consent is signed regardless of when these procedures may have been performed as part of routine clinical management.

The timing of each assessment is listed in the Time and Events Tables (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for safety, PK, PD/biomarker, immunogenicity, imaging or other assessments. Changes in timing, addition, or removal of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme. Up to approximately 350mL of blood will be collected over a 30-day period, including any extra assessments that may be required.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SPM.

After a subject has provided written informed consent for pre-screening, the investigator or other study personnel will determine if the subject is eligible for pre-screening in the study. This will be done by reviewing the pre-screening inclusion criteria (Section 5.2.1) and completing all of the pre-screening assessments outlined in the Time and Events Table (Section 7.1). Pre-screening assessments may be carried out over more than one day.

If during pre-screening the subject is determined to have the required HER3 or HER3 and NRG1 levels of expression then after a subject has provided written informed consent for the study and within 14 days of the first dose of study treatment, the investigator or other study personnel will determine if the subject is eligible for enrollment in the study. This will be done by reviewing the inclusion and exclusion criteria and completing all of the

screening assessments outlined in the Time and Events Tables (Section 7.1). Screening assessments may be carried out over more than one day provided that all required assessments are completed within14 days prior to the first dose of study treatment.

7.1. Time and Events Tables

This section consists of the Time and Events Tables and supplemental footnotes to describe assessment windows and sequencing of study-specific assessments and procedures.

Table 7 Time and Events for Part 1 (Dose Escalation Cohorts, every 2 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)			Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 8	Day 15				
		-14 day window[3]		± 1 day window for each visit			± 3 day window for each visit	+ 7 day window	
Informed consent	X	X							
Archival tissue	X								
Tumor biopsy	X[4]	X[5]			X[6] pre-dose			X[7]	
Skin biopsy			X pre-dose		X pre-dose				
Baseline demographics	X	X							
Medical history	X	X	X						
Concurrent medication	Continuous								
Pregnancy test[8]		X[3]				X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]		X	X	Every 4 weeks	X	
Height (at screening only) and weight		X	X			X	Weight: Every 4 weeks	X	
ECOG		X	X[9]			X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X	X	X	Every 2 weeks	X	
12-lead ECG		X	X[10]		X	X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]	X	X	X	Every 2 weeks	X	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated						

	Pre-screening	Screening	First Treatment Period (28 days)			Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 8	Day 15				
		-14 day window[3]		± 1 day window for each visit			± 3 day window for each visit	+ 7 day window	
Urinalysis		X				X	Every 4 weeks	X	
ECHO[11]		X				X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	Every 12 weeks	X	X
Safety cytokines[20]			In the event of infusion reaction						
Circulating cell free DNA (cfDNA)			X pre-dose					X[7]	
Testosterone and LH[13]			X pre-dose			X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X	X	X		X[7]	
GSK2849330 IV infusion[15]			X		X	X	Every 2 weeks[15]		
AE assessment			Continuous						
Serum sample for Immunogenicity			X pre-dose	X		X		X[16]	X[16]
PGx sample			X pre-dose[17]						
Tumor markers [18]			X				Every 8 weeks		
Disease assessment[19]		X[3]					Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh pre- and on-treatment tumor biopsy is optional, but strongly encouraged for dose escalation cohorts; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.

6. Tumor biopsy is optional on Day 15 for dose escalation cohort subjects and required for the PK/PD cohorts. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected for subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to the start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If the screening visit was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1hour (± 15-minute window), and 6 hour (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. Additional PK samples will be collected at Day 8, Day 15, and Day 29. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up and Post-study visits. Unless stated otherwise, on days of dosing sample will be drawn pre-dose. For the first subject in Cohort 1, additional PK samples will be taken at 24 hours (Day 2 [± 8-hours window]) and at 72 hours (Day 4 [± 24-hour window]) after the end of infusion of the first dose of GSK2849330.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For any subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2 week or every 3 week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules use the appropriate Time and Events Table as applicable.
16. After the first treatment period, immunogenicity samples will be collected every 12 weeks from the first dose within one year of treatment. If treatment continues after 1 year, samples will be collected every 24 weeks. An immunogenicity sample must be collected at both the Follow up and the Post-study visit.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.

20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression, disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.

Table 8 Time and Events for Part 1 (Dose Escalation Cohorts, every week dosing schedule)

	Pre-screen	Screen	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 2	Day 4	Day 8	Day 15	Day 22				
		-14 day window[3]	± 1 day window for each visit							±2 day window for each visit	+ 7 day window	
Informed consent	X	X										
Archival tissue	X											
Tumor biopsy	X[4]	X[5]					X[6] pre-dose				X[7]	
Skin biopsy			X pre-dose				X pre-dose					
Baseline demographics	X	X										
Medical history	X	X	X									
Concurrent medication	Continuous											
Pregnancy test[8]		X[3]							X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X						X	Weight: Every 4 weeks	X	
ECOG		X	X[9]						X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	X	X	Every week[22]	X	
12-lead ECG		X	X[10]				X		X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	X	Every week[22]	X	

	Pre-screen	**Screen**	**First Treatment Period (28 days)**						**Day 29**	**Continuation Phase**	**Follow-up[1]**	**Post-study[2]**
			Day 1	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 22**				
		-14 day window[3]			**± 1 day window for each visit**					**±2 day window for each visit**	**+ 7 day window**	
Coagulation parameters: PT, INR, PTT		X	As clinically indicated									
Urinalysis		X							X	Every 4 weeks	X	
ECHO[11]		X							X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction									
Circulating cell free DNA (cfDNA)			X pre-dose								X[7]	
Testosterone and LH[13]			X pre-dose						X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X			X	X		X		X[7]	
GSK2849330 IV infusion[15]			X			X	X	X	X	Every week[15]		
AE assessment			Continuous									
Serum sample for Immunogenicity			X pre-dose								X[16]	X[16]
PGx sample			X pre-dose[17]									
Tumor markers [18]			X							Every 8 weeks		
Disease assessment[19]		X[3]								Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.

3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh pre- and on-treatment tumor biopsy is optional, but strongly encouraged for dose escalation cohorts; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is optional on Day 15 for dose escalation cohort subjects and required for the PK/PD cohorts. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected for subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If the screening visit was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window) and 24 hours (± 8-hour window) after the end of infusion. Pre-dose samples will also be collected on Day 4 (± 1-day window), Day 8 (± 1-day window) and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter. If treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up and Post-study visits.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hr window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For any subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2 week or every 3 week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received Subsequent cohorts may receive different dosing schedules use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.

19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety biomarkers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression, disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

Table 9 Time and Events for Part 1 PK/PD Cohorts (every 2 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week								
			Day 1	Day 2	Day 4	Day 8	Day 15				
		- 14 day window[3]			± 1 day window for each visit				± 3 day window for each visit	+ 7 day window	
Informed consent	X	X									
Archival tissue	X										
Tumor biopsy	X[4]	X[5]					X[6] pre-dose			X[7]	
Skin biopsy			X pre-dose				X pre-dose				
Baseline demographics	X	X									
Medical history	X	X	X								
Concurrent Medication	Continuous									X	
Pregnancy test[8]		X[3]						X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X	X	Every 4 weeks	X	
Height (at screening only) and weight		X	X					X	Weight: Every 4 weeks	X	
ECOG		X	X[9]					X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]				X	X	Every 2 weeks	X	
12-lead ECG		X	X[10]				X	X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	Every 2 weeks	X	
Coagulation parameters: PT, INR, PTT		X	As clinically indicated								

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15				
			Day 1	Day 2	Day 4	Day 8					
		- 14 day window[3]			**± 1 day window for each visit**				**± 3 day window for each visit**	**+ 7 day window**	
Urinalysis		X						X	Every 4 weeks	X	
ECHO[11]		X						X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction								
cfDNA			X pre-dose							X[7]	
Testosterone and LH[13]			X pre-dose					X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X		X	X	X		X[7]	
GSK2849330 IV infusion[15]			X				X	X[15]	Every 2 weeks[15]		
AE assessment	Continuous										
Serum sample for Immunogenicity			X pre-dose							X[16]	X[16]
PGx Sample[17]			X pre-dose								
Tumor markers [18]			X						Every 8 weeks		
Disease assessment[19]		X[3]							Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 15 dose.

7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If the screening visit was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected Day 1: pre-dose and at1 hour (± 15-minute window), 6 hours (± 1-hour window) and 24 hours (± 8-hour window) after the end of infusion. Pre-dose samples will also be collected on Day 4 (± 1-day window), Day 8 (± 1-day window) and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window), and 24 hours (Day 2 [± 8-hr window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will be collected at progression.
15. The study treatment dosing window is ± 3 days for subjects on an every 2 week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample will be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression, disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.

Table 10 Time and Events for Part 1 PK/PD Cohorts (every week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22				
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]	± 1 day window for each visit							± 2 day window for each visit	+ 7 day window	
Informed consent	X	X										
Archival tissue	X											
Tumor biopsy	X[4]	X[5]					X[6] pre-dose				X[7]	
Skin biopsy			X pre-dose				X pre-dose					
Baseline demographics	X	X										
Medical history	X	X	X									
Concurrent Medication	Continuous										X	
Pregnancy test[8]		X[3]							X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X						X	Weight: Every 4 weeks	X	
ECOG		X	X[9]						X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	X	X	Every week[22]	X	
12-lead ECG		X	X[10]				X		X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	X	Every week[22]	X	

	Pre-screening	Screening	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22				
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]			± 1 day window for each visit					± 2 day window for each visit	+ 7 day window	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated									
Urinalysis		X							X	Every 4 weeks	X	
ECHO[11]		X							X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction									
cfDNA			X pre-dose								X[7]	
Testosterone and LH[13]			X pre-dose						X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X		X	X		X		X[7]	
GSK2849330 IV infusion[15]			X			X[15]	X	X	X[15]	Every week[15]		
AE assessment	Continuous											
Serum sample for Immunogenicity			X pre-dose								X[16]	X[16]
PGx Sample[17]			X pre-dose									
Tumor markers [18]			X							Every 8 weeks		
Disease assessment[19]		X[3]								Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.

3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 15 dose.
7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If the screening visit was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of infusion. For subjects on a weekly dosing schedule, vital signs should be conducted weekly at each dosing visit in clinic.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected Day 1: pre-dose and at1 hour (± 15-minute window), 6 hours (-± 1-hr window) and 24 hours (± 8-hour window) after the end of infusion. Pre-dose samples will also be collected on Day 4(± 1-day window), Day 8 (± 1-day window) and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hour (± 1-hour window), and 24 housr(Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will be collected at progression.
15. For the subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days The study treatment dosing window is ± 3 days for subjects on an every 2 week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.

19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression,disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

Table 11 Time and Events for Part 1 PK/PD Cohorts (every 3 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (21 days)					Continuation Phase	Follow-up[1]	Post-study[2]
			First Week							
			Day 1	Day 2	Day 4	Day 8	Day 22			
		- 14 day window[3]			± 1 day window for each visit			± 3 day window for each visit	+7 day window	
Informed consent	X	X								
Archival tissue	X									
Tumor biopsy	X[4]	X[5]					X[6]pre-dose		X[7]	
Skin biopsy			X pre-dose				X pre-dose			
Baseline demographics	X	X								
Medical history	X	X	X							
Concurrent medication	Continuous								X	
Pregnancy test[8]		X[3]					X pre-dose	Every 3 weeks	X	X
Physical examination		X	X[9]				X	Every 3 weeks	X	
Height (at screening only) and weight		X	X				X	Weight: Every 3 weeks	X	
ECOG		X	X[9]				X	Every 3 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	Every 3 weeks	X	
12-lead ECG		X	X[10]				X	Every 3 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	Every 3 weeks	X	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated							
Urinalysis		X					X	Every 3 weeks	X	
ECHO[11]		X					X	Every 9 weeks from day 22	X	

	Pre-screening	Screening	First Treatment Period (21 days)					Continuation Phase	Follow-up[1]	Post-study[2]
			First Week							
			Day 1	Day 2	Day 4	Day 8	Day 22			
		- 14 day window[3]			± 1 day window for each visit			± 3 day window for each visit	+7 day window	
PK (Blood)[12]			X	X	X	X	X	Day 43 and every 12 weeks	X	X
Safety cytokines[20]			In the event of infusion reaction							
cfDNA			X pre-dose						X[7]	
Testosterone and LH[13]			X pre-dose				X	Every 9 weeks from day 22		
Whole blood/serum /cellular markers[14]			X	X		X	X	Day 43	X[7]	
GSK2849330 IV infusion[15]			X				X	Every 3 weeks[15]		
AE assessment	Continuous									
Serum sample for Immunogenicity			X pre-dose						X[16]	X[16]
PGx Sample[17]			X pre-dose							
Tumor markers [18]			X					Every 9 weeks		
Disease assessment[19]		X[3]						Every 9 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and disease assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 22 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 22 dose.
7. Collected at progression. Tumor biopsy is optional and only required from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 22 and every 3 weeks from Day 22 in the continuation phase of the study.
9. If the screening visit was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.

10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 9 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. Additional PK samples will be collected at 24 hours (Day 2 [± 8-hr window]) and 72 hours (Day 4 [± 24-hour window]) after the end of infusion, and at Day 8 (± 1-day window and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 29 and 57. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will be collected at the Post-study visit. On days of dosing sample will be drawn pre-dose.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular marker. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hourwindow), and 24 hours (Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 22 and Day 43 for all cohorts. An additional blood sample should be collected at progression.
15. The study treatment dosing window is ± 3 days for an every 3-week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received.
16. An immunogenicity sample will be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression,disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.

Table 12 Time and Events for Part 2 Molecularly Defined Tumor Histology Groups

	Pre-Screen	Screen	First Treatment Period (28 days)				Day 29	Continuation Phase	Follow up[1]	Post study[2]
			Day 1	Day 8	Day 15	Day 22				
		-14 day window[3]		± 1 day window for each visit				± 2day window for each visit	+ 7 day window	
Informed consent	X	X								
Archival tissue	X									
Tumor biopsy	X[4]	X[5]			X[6] pre-dose				X[7]	
Baseline demographics	X	X								
Medical history	X	X	X							
Concurrent medication	Continuous									
Pregnancy test[8]		X[3]					X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]		X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X				X	Weight: Every 4 weeks	X	
ECOG		X	X[9]				X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X[22]	X	X[22]	X	Every week [22]	X	
12-lead ECG		X	X[10]		X		X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]	X[22]	X	X[22]	X	Every week[22]	X	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated							
Urinalysis		X					X	Every 4 weeks	X	
ECHO[11]		X					X	Every 8 weeks	X	

	Pre-Screen	Screen	First Treatment Period (28 days)				Day 29	Continuation Phase	Follow up[1]	Post study[2]
			Day 1	Day 8	Day 15	Day 22				
		-14 day window[3]		± 1 day window for each visit				± 2day window for each visit	+ 7 day window	
PK (Blood)[12]			X		X		X	X[12]	X	X
Safety cytokines[20]			In the event of an infusion reaction							
Circulating cell free DNA (cfDNA)			X pre-dose						X[7]	
Testosterone and LH[13]			X pre-dose				X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X[22]	X		X		X[7]	
GSK2849330 IV infusion[15]			X	X[22]	X	X[22]	X	Everyweek[15,22]		
AE assessment			Continuous							
Serum sample for Immunogenicity			X pre-dose						X[16]	X[16]
PGx sample			X pre-dose[17]							
Tumor markers [18]			X					Every 8 weeks		
Disease assessment[19]		X[3]						Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh pre- and on-treatment tumor biopsy is required; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.

8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If the screening visit was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. For vitals: collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion. For ECG: collect at pre-dose and 2 hours after the start of the first infusion
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), after the end of infusion, and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and every 12 weeks thereafter. If treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up or Post-study visits. Unless stated otherwise, on days of dosing sample will be drawn pre-dose.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer, the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For the subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2-week or every 3-week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression,disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

7.2. Demographic/Medical History and Baseline Assessments

Demographic data will include gender, age, race, height, and weight. Medical, surgical, and treatment history including date [month (if available) and year] of first diagnosis, best response to prior systemic therapy, histology, molecular characteristics and current sites of disease will be taken as part of the medical history and disease status. Details concerning concomitant medication will be recorded starting from screening through the follow-up visit. At a minimum, the drug name, route of administration, dose and frequency of dosing, along with start and stop dates/times should be recorded.

7.2.1. Critical Baseline Assessments

Cardiovascular medical history/risk factors will be assessed at baseline.

7.3. Safety Evaluations

Measurements used to evaluate safety will include physical examinations, vital signs (BP, temperature and pulse rate), 12-lead ECGs, echocardiography, clinical laboratory tests, , and monitoring for AEs. Planned time points for all safety assessments are provided in the Time and Events Tables (Section 7.1).

Additional, unplanned safety assessments may be performed during the course of the study as clinically indicated in the judgment of the investigator. Additional time points for safety tests may also be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Physical Examinations

A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), spine and long bones, lymph nodes and extremities. Height (at screening only) and weight will also be measured and recorded.

7.3.2. ECOG Performance Status

The performance status will be assessed using the ECOG scale (Appendix 3) as specified in the Time and Events Tables (Section 7.1).

7.3.3. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure (BP), temperature, and pulse rate. Vital signs will be measured more frequently if warranted by clinical condition of the subject. On days where vital signs are measured multiple times, temperature does not need to be repeated unless clinically indicated. Refer to the SPM for details regarding measurement of vital signs.

If a subject develops a fever within the immediate post-infusion period, refer to Section 3.9.1 and Section 3.9.2 for management of infusion reactions and allergic reactions.

7.3.4. Electrocardiogram

Single 12-lead ECGs will be obtained at designated time points during the study using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after the subject has at least a 5-minute rest and is in a semi-recumbent or supine position.

All ECGs will be single assessments unless clinically significant abnormality is observed, in which case repeat ECG twice more, for a total of 3 ECGs within approximately 5-15 minutes. Manual calculation for all 3 ECGs should be done using Fridericia's formula ($QTcF=QT/(RR)^{1/3}$) in view of the complex relationship between QT and RR. Any clinical decisions should be based on the average of all 3 ECGs.

Refer to Section 3.8.2 for QTc withdrawal criteria.

Refer to the SPM for details regarding ECG procedures.

7.3.5. Echocardiogram and/or Multi-gated Acquisition (MUGA) Scans

ECHO will be performed to assess cardiac ejection fraction as noted in the Time and Events Tables Section 7.1. Should electrocardiography not be available or if echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. However, whichever method is used at baseline should be used for the remaining assessments in the study. Additional ECHO assessments may be performed if clinically warranted. The evaluation of the echocardiographer should include an evaluation for LVEF.

Copies of all ECHOs performed on subjects who experience an absolute decrease >15% in LVEF compared to baseline or an absolute decrease >10% in LVEF compared to baseline concurrent with LVEF <50% may be required by GSK for review.

7.3.6. Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 13), should be performed according to the Time and Events Tables (Section 7.1). Details for the preparation and shipment of samples will be provided in the SPM.

At the discretion of the investigator, additional laboratory samples may be taken as clinically necessary. If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (for example SAE or AE or dose modification) the results must be recorded in the subject's eCRF.

All abnormal laboratory tests with values that are clinically significant during study participation or within 28 days after the last dose of study treatment should be repeated until the values return to within normal range or baseline or the subject starts subsequent treatment. All subjects who have a Grade 3 or 4 laboratory abnormality at time of study withdrawal must be followed until resolution to Grade 2 or less, unless it is unlikely to improve due to underlying disease or subsequent therapy.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Table 13 List of Clinical Laboratory Tests

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
Red blood cell (RBC) Count	Mean corpuscular volume (MCV)	Neutrophils	
White blood cell (WBC) Count (absolute)	Mean corpuscular hemoglobin (MCH)	Lymphocytes	
Reticulocyte Count	Mean corpuscular hemoglobin concentration (MCHC)	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Clinical Chemistry			
Blood urea nitrogen (BUN) or urea	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Glucose, fasting	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other tests			
PT, INR, PTT			
Testosterone (male subjects only)			
Luteinizing Hormone (LH) (male subjects only)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

7.3.7. Pregnancy Testing and Reporting

All pregnancies in female subjects and/or female partners of male subjects will be collected after the start of dosing and until the post-study visit.

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

If a female subject is of childbearing potential, she must have a serum Beta-human chorionic gonadotropin (β-HCG) pregnancy test performed within 7 days prior to the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below during the study until 45 days or 5 half-lives (whichever is longer) following the last dose of study treatment. Additional pregnancy tests will be performed as outlined in the Times and Events Table (see Section 7.1).

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

In addition, the investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to GSK as described above.

7.4. Pharmacokinetics

For subjects enrolled in Part 1, dose escalation Cohorts 1-4, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour and 6 hoursafter the end of infusion and at Day 8, Day 15, and Day 29 after the first dose of GSK2849330. If a subject's duration of infusion is 3 hours or longer, the 6-hour time point is optional. On days of dosing, the sample will be drawn pre-dose. Additionally the first subject in Cohort 1 will have PK samples taken at 24 hour (Day 2) and 72 hour (Day 4) after the end of infusion.

For cohorts enrolled under Amendment 1 of this protocol, more frequent PK samples will be collected on Day 1: pre-dose and at 1 hour, 6 hours and 24 hours after the end of infusion;. Pre-dose samples will also be collected on Day 4, Day 8, and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85, and every 12 weeks thereafter.

For all subjects in the Part 1 PK/PD cohorts, blood samples for analysis of GSK2849330 concentrations will be collected on scheduled dosing Days 1: pre-dose and at 1 hour, 6 hours and 24 hours after the end of infusion. Pre-dose samples will also be collected on Day 4, Day 8, and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.

For the molecularly defined tumor histology groups in Part 2, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour after the end of infusion; and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and every 12 weeks thereafter.

For all subjects (Part 1 and Part 2), if treatment continues beyond 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up visit (28 days after the last dose of study treatment),and/or the Post study visit (45 days or 5 half-lives [whichever is longer] after the last dose of study treatment). Unless stated otherwise, on days of dosing PK samples will be drawn pre-dose.

See the Time and Events Tables Section 7.1 and the SPM for additional details on the PK sample timing.

7.4.1. Blood Sample Collection for Pharmacokinetics

Blood samples for PK analysis of GSK2849330 will be collected at the time points indicated in the Time and Events Tables (Section 7.1). Each PK sample should be collected as close as possible to the planned time relative to the dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Once preliminary PK data have been reviewed, the planned sample collection times may be revised and provided to sites in writing. Changes in PK sample collection times will not constitute a protocol amendment.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SPM.

7.4.2. Pharmacokinetic Sample Analysis

Plasma analysis will be performed under the management of Bioanalytical Science and Toxicokinetics, Drug Metabolism and Pharmacokinetics (DMPK), GSK. Concentrations of GSK2849330 will be determined in plasma samples using the currently approved analytical methodology. Raw data will be stored in the GLP Archives, GSK.

7.5. Immunogenicity

7.5.1. Blood Sample Collection

Serum samples for determination of anti- GSK2849330 antibodies will be taken from all subjects in this study at the time-points specified in the Time and Events Tables in Section 7.1.

7.5.2. Sample Analysis

Samples will be analyzed for the presence of anti-GSK2849330 antibodies using a validated immunoelectrochemiluminescenceassay. The assay involves screening, confirmation and titration steps (tiered-testing approach). Confirmed positive samples will be titrated to obtain the titer of the anti-GSK2849330 antibodies. Further antibody characterization may be performed, if needed. Results will-be reported at the end of the study. Details on sample preparation, storage and analysis will be given in the SPM.

7.6. Translational Research

Unless stated otherwise, these investigations may be performed irrespective of whether a response to GSK2849330 is observed.

Comparative examination of pre-dosing profiles of participants may uncover known or novel candidate biomarkers/profiles which could be used to predict response to treatment with GSK2849330 or provide new insights into cancer and medically related conditions. Comparative examination of post-dosing profiles with pre-dosing profiles may yield known and novel candidate biomarkers/profiles and new insights which relate directly or indirectly to the mechanism of action of GSK2849330.

All samples may be retained for a maximum of 15 years after the last subject completes the study.

Novel candidate biomarkers and subsequently discovered biomarkers of the biological response associated with cancer or medically related conditions and/or the action of GSK2849330 may be identified by application of:

- DNA/gene, RNA, protein and cell population analysis of tumor/skin tissue.
- Circulating cell free-DNA analysis of blood/plasma.
- Circulating/peripheral biomarkers
    - Cytokines and Angiogenic Factors (CAF) analysis of plasma
    - Proteome analysis of plasma
    - Complement CH50 analysis of serum
    - Peripheral blood mononuclear cell (PBMC) count analysis of whole blood

RNA transcriptome research and/or RNA expression research on whole of a subset of RNA species are included as relevant for the study.

7.6.1. Tumor Biomarker Analysis

7.6.1.1. Tumor Tissue for Pre-screening Assessments and Exploratory Research

Tumor tissue taken from a metastatic site (preferably) or obtained at the time of primary cancer diagnosis (biopsy or from definitive surgery) is required to be submitted for analysis to one or more of the central laboratories, including Ventana Medical Systems to determine HER3 and NRG1 expression. If archival tumor tissue is not available, a fresh biopsy using a procedure that is safe for the subject is required for HER3 and NRG1 testing.

Refer to the SPM for further details on tumor tissue sample requirements preparation and shipping.

Additional exploratory research may include the evaluation of intra-tumoral molecular profiles (to include RNA, DNA/gene, protein, and cell populations) that may uncover known or novel candidate biomarkers/profiles that could be used to predict response to GSK2849330 or possibly glean biological information into its mechanisms of action.

Histological features may be evaluated to include but are not limited to the enumeration of cell type populations such as lymphocytes.

7.6.1.2. Tumor Biopsies

Every effort should be made to collect pre- and on-treatment tumor biopsies using a procedure that is safe for the subject. Image guidance has been shown to significantly increase the probability of success in obtaining tumor biopsies and is required for all percutaneous pre- and on-treatment biopsies in this study (with the exception of melanoma skin lesions or cutaneous metastases of other solid tumors).

Tumor biopsies are optional for subjects in the dose escalation cohorts, but strongly encouraged. All subjects enrolled in PK/PD cohorts in Part 1 and in each of the molecularly defined tumor histology groups in Part 2 must agree to pre and on-treatment tumor biopsies (using a procedure that is safe for the subject) for assessment of PD effect. GSK will closely monitor and evaluate the collection of evaluable biopsies and will notify the participating centers of any change to the collection requirements for any or all groups.

Tumor biopsies for PD analyses will be collected at the time points listed in the Time and Events Tables Section 7.1.

Tumor biopsies should be obtained upon disease progression, using a procedure that is safe for the subject, if the subject provides consent, and if the tumor is in a biopsy-accessible location. Once preliminary PK and PD data have been reviewed, the planned tumor biopsy collection times may be revised and provided to sites in writing. Changes in sample collection times will not constitute a protocol amendment.

Biopsies may be analyzed for genetic markers (mutations in genes to potentially include but not limited to PIK3CA, PTEN, and BRAF), DNA, RNA or protein levels that may indicate a PD response, or correlate with a tumor response, to GSK2849330. Protein levels that may be analyzed include, but are not limited to, markers of the HER3 pathway such as HER3, phospho-HER3 and HER3 ligands (neuregulins); markers of cell proliferation such as Ki67; markers of ADCC such as perforin and granzyme B; markers of the CDC pathway; and markers of tumor resistance such as the PTEN protein. Additional analyses may include the evaluation of histological features to include but are not limited to the enumeration of cell type populations such as lymphocytes.

Details on tumor biopsy collection, processing, storage and shipping procedures are provided in the SPM.

7.6.2. Skin Biopsies

For subjects in Part 1 of the study, every effort should be made to collect pre- and on-treatment skin biopsies for analysis of RNA or protein levels that may indicate a PD response to GSK 2849330. Protein levels that may be analyzed include, but are not limited to, markers of the HER3 pathway such as HER3 and phospho-HER3.

All subjects enrolled in dose escalation and PK/PD cohorts in Part 1 must agree to pre and on-treatment skin biopsies for assessment of PD effect.

Refer to Time and Events Tables in Section 7.1 for details on time points.

Details on skin biopsy collection, processing, storage and shipping procedures are provided in the SPM.

7.6.3. Blood Samples

Blood-based markers have the important advantage that specimens are readily available, simple to prepare and store, and can be taken prior to and during treatment. This allows for the assessment of predictive markers based on the baseline evaluation as well as markers of activity and resistance based on changes that occur during treatment.

Blood samples will be collected for analysis of potential surrogate markers of GSK2849330 activity. These analyses may include, but are not limited to measurement of specific blood proteins and cell populations (e.g., PBMCs: CD16, CD56, CD69, CD107, CD19, CD8, CD4, CD3, CD14), complement activity (e.g., CH50), inflammatory cytokines (e.g., IFNγ, TNFαIL-2, IL-6), growth factors, soluble HER3, or mutations in circulating free tumor DNA (Refer to Section 7.6.3.1).

Blood samples drawn for investigating both predictive and PD biomarkers will be by study part and subject cohort or group:

Details on sample collection, processing, storage and shipping procedures are provided in the SPM.

7.6.3.1. Circulating Cell-free DNA (cfDNA) Analysis

Tumor-specific cfDNA levels detected in plasma or serum have been found to correlate with increasing tumor burden and decline following therapy. Furthermore, cfDNA in cancer subjects can harbor many genetic alterations (mutations, microsatellite alterations, aberrant methylation), which are generally consistent with the tumor. Thus, tumor-specific circulating cfDNA has the potential to be a useful biomarker of therapeutic response as well as offering a less invasive blood based technique for identifying and selecting subjects for certain treatments. Given the promise of cfDNA blood based test for subject selection, this test will be explored to determine whether mutations in cfDNA that may include but are not limited to PIK3CA, PTEN, and BRAF, correlate with the mutations in the tumor. This test will also be explored to correlate increasing cfDNA levels with increasing tumor burden. These mutations will be specific to the primary tumor types enrolled in the study.

7.6.3.2. Cytokines Analysis

A panel of inflammatory cytokines which may include but are not limited to IFNγ, TNFα, IL6, IL2, and MCP-1 will be evaluated in plasma and correlated with clinical outcome of treatment with GSK2849330.

7.7. Pharmacogenetics (PGx)

An important objective of the clinical study is PGx research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Subjects who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in selected candidate genes, such as but not limited to the FCγ receptor family, in DNA from blood may be analyzed to determine their relationship with response (safety, tolerability, PK and efficacy to treatment with GSK2849330).

Information regarding PGx research is included in Appendix 8. The IRB/EC and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 8). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore PGx assessments will not be conducted.

7.8. Evaluation of Anti-Cancer Activity

Disease assessment may include imaging (e.g., CT scan, MRI, bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). Disease assessment will be completed within 4 weeks prior to the first dose of GSK2849330, then every 8 or 9 weeks thereafter, and at the final study visit. See the Time and Events Tables (Section 7.1) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study, progressive disease (PD) has not been documented, and the subject has not started subsequent anti-cancer therapy, a disease assessment should be obtained at the Follow-up visit or the Post-study visit.

In addition to the above, a MRI with contrast should be considered to rule out the presence of brain metastases. CT scans with and without contrast may be performed if a MRI is contraindicated or otherwise unavailable.

For purposes of determining futility, disease progression and response evaluations will be determined according to the definitions established in the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [Eisenhauer, 2009] (see Appendix 5). Exploratory assessment of response according to immune-related response criteria (Appendix 6) and mRECIST (Appendix 7) [Lencioni, 2010] should also be recorded. Subjects whose disease responds (either CR or PR) should have a confirmatory disease assessment performed at least 4 weeks after the date of assessment during which the response was demonstrated. More frequent disease assessments may be performed at the discretion of the investigator. To ensure comparability between the baseline and subsequent assessments, the same method of assessment, the same technique and the same radiologist should be used when assessing response. Images should be retained until study completion to facilitate central review if requested. Tumor markers should be followed serially per institutional guidelines and recorded in the eCRF where part of standard practice.

8. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 8.1 and Section 8.2, respectively.

8.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally

associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose *per se* will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

8.2. Definition of an SAE

A SAE is any untoward medical occurrence that, at any dose:

Results in death

a. Is 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, which hypothetically might have caused death, if it were more severe.

b. Requires hospitalization or prolongation of existing hospitalization

   NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are

AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

c. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

d. Is a congenital anomaly/birth defect.

e. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

f. Protocol-Specific SAEs:

- All events of possible study treatment-induced liver injury with hyperbilirubinemia defined as ALT ≥3 times ULN **and** bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured) or termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants).

  NOTE: Bilirubin fractionation is performed if testing is available. If testing is not available, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥2 times ULN, then the event is still reported as a SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

- LVEF (Section 3.8.3.1): meeting stopping criteria.

8.2.1. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. The GSK Medical Monitor is accountable for reviewing all SAEs for possible Sentinel Events which is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible

Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired long QT syndrome
- Agranulocytosis/severe neutropenia
- Anaphylaxis & anaphylactoid reactions (see Section 3.9.2 on Allergic Reaction Management)
- Hepatotoxicity
- Acute renal failure
- Seizure
- Stevens-Johnson syndrome/toxic epidermal necrosis

8.3. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

In addition, an associated AE or SAE is to be recorded for any laboratory test result or other safety assessment that led to an intervention, including permanent discontinuation of study treatment, dose reduction, and/or dose interruption/delay.

Any new primary cancer must be reported as a SAE.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

8.3.1. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack

- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

8.4. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as a SAE. Death due to disease under study is to be recorded on the Death electronic case eCRF. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design or procedures and the disease progression, then this must be reported as a SAE.

8.5. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time the first dose of study treatment is administered until 28 days following discontinuation of study treatment.

SAEs will be collected over the same time period as stated above for AEs. In addition, any SAE assessed **as related** to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy), study treatment or GSK concomitant medication must be recorded from the time a subject consents to participate in the study up to and including any follow-up contact. All SAEs will be reported to GSK within 24 hours, as indicated in Section 8.5.2.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after 28 days the investigator may report any AE that they believe possibly related to study treatment.

8.5.1. Method of Detecting AEs and SAEs

Care must be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

“How are you feeling?” or for pediatric studies, “How does your child seem to feel?”

"Have you had any (other) medical problems since your last visit/contact?" or for pediatric studies, "Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?"

"Have you taken any new medicines, other than those provided in this study, since your last visit/contact?" or for pediatric studies, "Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?"

8.5.2. Prompt Reporting of SAEs and Other Events to GSK

SAEs, pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

	Initial Reports		**Follow-up Information on a Previous Report**	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
"CV events" and/or "death"	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	"CV events" and/or "death" data collection tool(s) if applicable	Initial and follow up reports to be completed within one week of when the cardiovascular event or death is reported	Updated "CV events" and/or "death" data collection tool(s) if applicable
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow-up Form
Liver chemistry abnormalities:				
ALT ≥3 times ULN and bilirubin ≥2 times ULN (>35% direct) (or ALT ≥3 times ULN and INR >1.5, if INR is measured)[c]	24 hours[a]	SAE data collection tool; Liver Event eCRF and liver imaging and/or biopsy eCRFs if applicable[b]	24 hours	Updated SAE data collection tool. Updated Liver Event eCRF[b]
ALT ≥5 times ULN; ALT ≥3 times ULN with hepatitis or rash or 3 times ULN ≥4 weeks	24 hours[a]	Liver Event eCRF[b]	24 hours	Updated Liver Event eCRF[b]
ALT ≥3 times ULN and <5 times ULN and bilirubin <2 times ULN	24 hours[a]	Liver Event eCRF does not need to be completed unless elevations persist for 4 weeks or subject cannot be monitored weekly for 4 weeks[b]		

a. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
b. Liver event documents should be completed as soon as possible.
c. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

See Section 3.8.1 for liver chemistry stopping criteria and follow up procedures.

Methods for detecting, recording, evaluating, and following up on AEs and SAEs are provided in the SPM.

8.5.3. Regulatory Reporting Requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/EC, if appropriate according to local requirements.

9. LIVER CHEMISTRY FOLLOW-UP PROCEDURES

9.1. Liver Chemistry Testing Procedures

For subjects meeting any of the liver chemistry stopping criteria in Section 3.8.1, make every attempt to carry out the **liver event follow-up assessments** described below:

- Viral hepatitis serology, including:
  - Hepatitis A IgM antibody
  - Hepatitis B surface antigen and hepatitis B core antibody (IgM)
  - Hepatitis C RNA
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, then obtain heterophile antibody or monospot testing)
- Blood sample for PK analysis, obtained within 10 days of the last dose of study drug(s). Record the date and time of the PK blood sample draw and the date and time of the last dose of study drug(s) prior the blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date or time of the last dose cannot be approximated, or if a PK sample cannot be collected within the 10-day period following the last dose, do not obtain a PK sample. Instructions for sample handling and shipping are found in the SPM.
- Serum creatinine phosphokinase (CPK) and lactate dehydrogenase (LDH).

- Fractionate bilirubin, if total bilirubin ≥2 X ULN.
- Obtain a complete blood count (CBC) with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms indicative of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia as relevant on the AE eCRF.
- Record the use of concomitant medications, including acetaminophen, herbal remedies or any other over the counter (OTC) medications, or any putative hepatotoxins, on the concomitant medication eCRF.
- Record alcohol use on the liver event alcohol intake eCRF.

The following assessments are required for subjects with ALT ≥3 X ULN and bilirubin ≥2X ULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Liver imaging (ultrasound, MRI or CT) to evaluate liver disease.

9.2. Liver Chemistry Monitoring Criteria

For subjects with ALT ≥3 X ULN **but** <5X ULN **and** bilirubin <2 X ULN, without symptoms indicative of hepatitis or rash, and who can be monitored safety for 4 weeks, the following actions should be taken:

- Notify the GSK Medical Monitor within 24 hours of learning of the abnormality to discuss subject safety.
- Continue administration of study drug(s).
- Evaluate liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) weekly until they resolve, stabilize or return to within baseline levels.
- If at any time the subject meets any of the liver chemistry stopping criteria 1 to 5 (Section 3.8.1), then proceed as described in Section 9).
- If, after 4 weeks of monitoring, ALT <3X ULN and bilirubin <2 X ULN, then monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

9.3. Drug Restart/Rechallenge Following Liver Events that are Possibly Related to Study Drug(s)

Approval by the GSK Medical Monitor to restart/rechallenge study drug(s) may be considered where:

- The subject is receiving compelling benefit, the benefit exceeds the risk, and no effective alternative therapy is available. Approval of restart/rechallenge by the IRB or Independent Ethics Committee (IEC) must be obtained, as required.

- If the restart/rechallenge is approved by GSK in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the GSK Medical Monitor.
- Subjects approved by GSK for restart/rechallenge of study drug(s) must return to the clinic twice a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.

9.4. Drug Restart Following Transient, Resolving Liver Events Not Related to Study Drug(s)

Approval by the GSK Medical Monitor to restart study drug(s) may be considered where:

- Liver chemistry abnormalities have a clear underlying cause (e.g., biliary obstruction, hypotension) and liver chemistries have improved to normal or are within 1.5 X baseline and ALT <3X ULN. Approval of restart by the IRB or IEC may be required.
- If the restart/rechallenge is approved by GSK in writing, then the subject must be provided with a clear description of the possible benefits and risks of administration of study drug(s), including the possibility of a recurrence, a more severe liver injury or death.
- The subject must also provide signed informed consent specifically for the study drug(s) restart/rechallenge. Documentation of the informed consent must be recorded in the subject's study chart.
- Study drug(s) must be administered at the dose specified by the GSK Medical Monitor.
- Subjects approved by GSK for restart/rechallenge of study drug(s) must return to the clinic once a week for evaluation of liver chemistry tests until stable liver chemistries have been demonstrated and laboratory monitoring may resume per protocol.
- If protocol-defined stopping criteria for liver chemistry abnormalities are met, study drug(s) administration must stop.

10. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Subjects will be instructed to inform the investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (Final Study Visit). Any concomitant medication(s), including non-prescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. Additionally, a complete list of all prior anti-cancer therapies will be recorded in the eCRF.

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by GSK and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

10.1. Permitted Medication(s)

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Growth factors (e.g., G-CSF) are not permitted during the DLT observation period in Part 1, but may be allowable beyond the DLT observation period in Part 1, in the PK/PD cohorts or in Part 2 after discussion with the GSK medical monitor.

The use of anticoagulant and antiplatelet agents are permitted. However, prior to undergoing tumor biopsy, it is recommended that subjects be off agents such as coumadin or heparin for 5 days and then recheck labs prior to biopsy procedure. It is further recommended that subjects be off of NSAIDs for at least 48 hours. If institution guidelines require these agents be held longer than the recommended number of days/ hours, then follow institution guidelines. If there are risks of stopping these medications, contact the GSK Medical Monitor.

10.2. Prohibited Medication(s)

Subjects should not receive other anticancer therapy (cytotoxic, surgery, tumor embolization, biologic, radiation, or hormone other than replacement) except where noted in the eligibility criteria while on treatment in this study.

If corticosteroids are needed for chronic conditions, doses below 20 mg/day of prednisone or the equivalent are allowed. Corticosteroids exceeding this level are generally not allowed except as infusion pre-medication.

11. LIFESTYLE AND/OR DIETARY RESTRICTIONS

11.1. Contraception

11.1.1. Female Subjects

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a FSH value >40 mIU/mL and an estradiol value < 40 pg/mL (<140 pmol/L).

A female of childbearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

Female subjects of childbearing potential must not become pregnant during the study and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of <1%.

Abstinence

Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.

Contraceptive Methods with a Failure Rate of <1%

- Oral contraceptives (either combined or progesterone only) if not contraindicated for this subject population or per local practice.
- Estrogenic vaginal ring if not contraindicated for this subject population or per local practice.
- Percutaneous contraceptive patches if not contraindicated for this subject population or per local practice.
- Implants of levonorgestrel if not contraindicated for this subject population or per local practice.
- Injectable progesterone if not contraindicated for this subject population or per local practice.
- Intrauterine device or intrauterine system that meets the <1% failure rate as stated in the product label.

- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, "documented" refers to the outcome of the investigator's/designee's medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject's medical records.
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus vaginal spermicidal agent (foam/gel/film/cream/suppository).

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects understand how to properly use these methods of contraception.

11.1.2. Male Subjects

To prevent pregnancy in a female partner or to prevent exposure of any partner to the study treatment from a male subject's semen, male subjects must use one of the following contraceptive methods:

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are <u>not</u> acceptable methods of contraception.

  Complete abstinence from sexual intercourse for 14 days prior to first dose of study treatment, through the dosing period, and for at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
- Condom *(during non-vaginal intercourse with any partner - male or female)* **OR**
- Double-barrier method: condom and occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository) *(during sexual intercourse with a female).*

11.2. Lactation Restrictions

Female subjects who are lactating must discontinue nursing prior to the first dose of study treatment and must refrain from nursing throughout the treatment period and for at least 45 days or 5 half-lives (whichever is longer) following the last dose of study treatment.

12. DATA MANAGEMENT

For this study, data will be collected using defined eCRFs, transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data. AEs and concomitant medications terms will be

coded using Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSK Drug. eCRFs, including queries and audit trails, will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

When laboratory samples (i.e., hematology and clinical chemistry) are analyzed by a central laboratory the results will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times. When laboratory samples are analyzed by a local laboratory, the laboratory normal ranges will be provided to GSK and the results will be entered into the eCRF.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

13. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

13.1. Hypothesis(es)

13.1.1. Part 1: Dose-Escalation Phase

With respect to primary objectives and endpoints, no specific hypotheses are being tested during the dose escalation portion of this study. The primary focus will be on determining the safety profile of GSK2849330 and recommended dose for further exploration. Most of the analyses will be descriptive or exploratory.

13.1.2. Part 2: Molecularly-Defined Tumor Histology Groups

For the groups in Part 2, hypothesized clinical benefit rates are provided in Section 13.2.2. A test that the clinical benefit rate is less than or equal to the null hypothesis rate versus the clinical benefit rate is greater than or equal to the alternative rate is being performed using the stopping rules provided. Descriptive statistics will be used to describe the observed response rates at the dose used in each of the groups.

13.2. Sample Size Determination

13.2.1. Part 1: Dose-Escalation Phase

The total number of subjects in the Part 1 dose escalation will depend on the number of dose escalations needed, but the minimum number of subjects anticipated to complete dose escalation is 13 and the anticipated number of subjects is approximately 34 subjects. The selection of sample size 34 is based on the goal of fully exploring available dose ranges for purposes of selecting an appropriate regimen(s) for Part 2. This will include a number of cohorts to establish an initial understanding of the dose-response relationship as well as to evaluate a range of PD biomarkers that may reveal the biological activity of GSK2849330. The initial cohort (1.4 mg/kg) will have 1 subject and Cohorts 2 through 5 will have 3 subjects in the dose escalation phase and up to an additional 3 subjects with

evaluable pre- and on-treatment paired biopsies in each of these cohorts for the PK/PD cohorts. See Section 3.3 and Table 3 for additional details. The actual number of cohorts and subjects will depend in part on the observed toxicity and the PK and PD observed during the dose escalation.

Simulations were conducted to determine the average sample size and percentage of time each dose was selected under 3 different scenarios: almost no toxicity scenario, little toxicity scenario and moderate toxicity scenario. For each scenario, 5000 clinical trials were simulated using the planned doses. Details are provided in Table 14.

The specified prior probabilities discussed in Section 3.3 were used to determine an explicit equation for the prior distribution using the FACTS software. The parameters (s.d.) of the explicit distribution are α=-5.334(1.9913), ln(β)=-0.0579 (0.1018), and ρ=-0.9977 where α and ln(β) are distributed as bivariate normal with correlation ρ.

Table 14 Simulation Results for Various Scenarios

Dose (mg/kg)	Scenario 1: Almost No Toxicity		Scenario 2: Little Toxicity		Scenario 3: Moderate Toxicity	
	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)	True DLT Rate	Percent of Trials Selecting Dose as MTD (%)
1.4	0.00005	0	0.0005	0.8	0.05	5.2
3	0.0005	0	0.1	10	0.1	14.2
10	0.005	0.2	0.2	33	0.2	37.4
30	0.055	99.8	0.25	56.2	0.3	43.2

The average sample size over the 5000 clinical trials simulated under Scenarios 1-3 was 15.2, 15.5, and 15.1 respectively.

13.2.2. Part 2: Molecularly-Defined Tumor Histology Groups

Once the recommended dose(s) and schedule(s) is/are confirmed from Part 1, at least 12 and up to 30 subjects per group will be enrolled at that dose(s) in Part 2, guided by decision rules defined in Section 13.6.2. These guidelines are based on the predictive probabilities of success if enrollment were to continue to 30 subjects using the methodology of [Lee, 2008].

The null hypothesis is:

$$H_0: p \leq 10\%$$

The alternative hypothesis is:

$$H_A: p \geq 30\%$$

Starting with a group of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 94% power. Group enrollment will be stopped early for futility if the predictive probability of success is less than 6%. The trial would not stop early for success. The Bayesian Prior was Beta (0.2, 0.8), a weak prior with a mean response rate of 20%. The group outcome will be considered successful if the posterior probability of (P >0.10 | observed data) is ≥80%. The futility boundary described in Section 13.6.2 was calculated based on the optimizing criterion of maximizing the power under the alternative hypothesis.

Under the null hypothesis, the expected sample size is 20 subjects and the probability of early termination is 77%. Under the alternative hypothesis, the expected sample size is 29 subjects and the probability of early termination is 5%.

13.3. Sample Size Sensitivity

No analysis of sample size sensitivity was performed.

13.3.1. Sample Size Re-estimation

Sample size re-estimation is not planned for this study.

13.4. Data Analysis Considerations

Data will be listed and summarized according to GSK integrated data standards library (IDSL) reporting standards where applicable. Complete details will be provided in the RAP.

13.4.1. Analysis Populations

The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2849330. Safety will be evaluated based on this analysis population.

The **Efficacy Population** will consist of all subjects from the All Treated Population for whom at least one post-dose tumor assessment by CT scan has been performed.

The **PK Population** will consist of all subjects from the All Treated Population for whom at least one post-dose PK sample is obtained and analyzed.

Additional analysis populations may be defined in the RAP.

13.4.2. Analysis Data Sets

The construction of datasets relating to the reporting and analysis of study data will be performed in accordance with all applicable GSK standards and procedures.

13.4.3. Withdrawal

Reason for subject withdrawal will be listed.

13.4.4. Missing Data

Missing data will not be imputed. Where appropriated, available data will be summarized over specified intervals (*e.g.,* from start of treatment until withdrawal from study) using suitable summary statistics.

13.4.5. Derived and Transformed Data

The PK parameters, AUC, Cmax, and MRT will be log-transformed prior to analysis.

13.4.6. Assessment Windows

Safety assessments that occur prior to the administration of study drug will be considered screening assessments. Safety assessments that occur after dosing has begun will be considered as having occurred while on treatment.

Disease assessments will be distinguished as belonging to either screening, continued therapy or post-study phases of the study.

13.4.7. Other Issues

Data from participating centers will be pooled prior to analysis. It is anticipated that subject accrual may be limited across centers and summaries of data by center would likely not be informative. Therefore, these summaries will not be provided.

Demographic and baseline characteristics will be summarized.

For PK analyses, assay values below the quantitative limit (BQL) will be handled as described in the GSK CPK/M&S PK methods.

13.5. Treatment Comparisons

13.5.1. Primary Comparisons of Interest

Several dose levels and regimens of GSK2849330 are being investigated. No formal comparisons will be performed regarding differences between the dose levels. Safety, PK, PD biomarker, and clinical benefit summaries will be provided by dose level of GSK2849330.

13.5.2. Other Comparisons of Interest

In Part 1, PK parameters including, but not limited to, AUC(0-t), AUC(0-τ), AUC(0-∞), Cmax, tmax, and MRT of GSK2849330 will be descriptively compared between dose

levels in tabular or graphic formats. In Part 2, other safety, PK and clinical activity data than the primary endpoints will also be evaluated and compared between different treatment groups.

- PK: PK parameters including, but not limited to, AUC(0-t), AUC(0-τ), AUC(0-∞), Cmax, tmax, and MRT of GSK2849330 will be descriptively compared between dose levels in tabular or graphic formats.
- PD biomarker: Changes from baseline in PD markers, the markers of inflammatory response activation from blood and markers in skin and tumor biopsies will be evaluated and summarized for each dose cohort or group.
- Clinical anti-cancer activity: The number of CRs, PRs, stable diseases (SDs) and PDs for each dose cohort or group will be listed using RECIST, irRC, and mRECIST and summarized if appropriate.

13.6. Interim Analysis

Ongoing examination of safety, PK and PD data will occur while the study is being conducted. In Part 1, PK parameters will also be evaluated and compared among different treatment cohorts.

13.6.1. Part 1: Dose-Escalation

In Part 1 (Dose-Escalation), an interim analysis will be performed to determine if a dose-escalation is appropriate and to be informed of the data reviewed to support the dose-escalation decision following the completion of each dose cohort. The primary driver for the dose-escalation decision(s) in Part 1 will be safety and tolerability of each dose cohort. Further details regarding such analyses will be provided in the RAP.

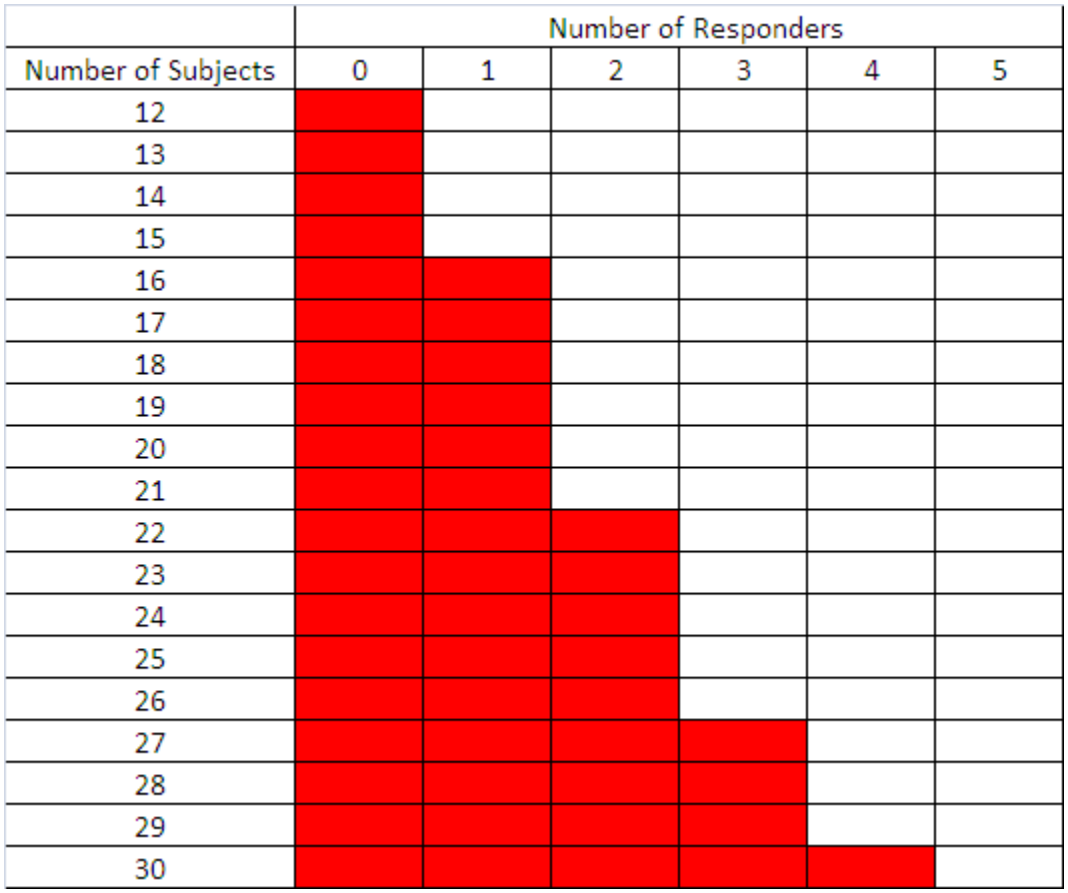
13.6.2. Part 2: Molecularly Defined Tumor Histology Groups

For each of the groups in Part 2, response data will be reviewed on an ongoing basis. After the initial 12 subjects have been enrolled at the recommended dose, the number of responses observed will be compared with the stopping rules provided in Table 15 and Figure 1 below.

Table 15 xStopping rules for each expansion group

Number of Subjects Enrolled	Stop for Futility if ≤ this number of responders is observed
12	0
16	1
22	2
27	3
30	4

Figure 1 Diagram of Stopping Rules for each Group



13.7. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or

additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

As the duration of treatment for a given subject will depend on efficacy and tolerability, the duration of follow-up will vary between subjects. Consequently there will be no imputation for missing data.

Demographic and baseline characteristics will be summarized.

13.7.1. Anti-Cancer Activity Analyses

The Efficacy Population will be used for anti-cancer activity analyses. Since this is a Phase I study, anti-cancer activity will be evaluated based on clinical evidence and response criteria. Where appropriate, the lesion data will be listed for each subject. The percent change from baseline will be calculated for each subject and listed, along with their ORR, CR, PR, SD and PD according to standard RECIST 1.1 (See Appendix 5). mRECIST and irRc will be calculated and listed as applicable. Response data will be summarized by cohort or group. If data warrant, the response data will be summarized by dose level. Response-evaluable subjects are defined as subjects with a pre-dose and at least 1 post-dose disease assessment. Correlation analysis may be conducted to explore any relationship between the subject's tumor type specific markers and tumor response based on RECIST, version [1.1], mRECIST and irRc. Other measures of clinical benefit specific to the groups in Part 2 will be summarized by group as appropriate.

Full details will be specified in the RAP.

13.7.2. Safety Analyses

The All Treated Population will be used for the analysis of safety data. All serially collected safety endpoints (e.g., laboratory tests, vital signs, ECGs) will be summarized according to the scheduled, nominal visit at which they were collected and across all on-treatment time points using a "worst-case" analysis.

DLTs will be listed for each subject and summarized according to GSK IDSL standards. All other relevant safety data will be listed and summarized according to the GSK IDSL standards as well. Complete details of the safety analyses will be provided in the RAP.

13.7.2.1. Extent of Exposure

Extent of exposure of GSK2849330 will depend on tolerability of the subjects to the doses administered and the course of their disease.

The number of subjects administered study treatment will be summarized according to the duration of therapy.

13.7.2.2. Adverse Events

AEs will be coded using the standard MedDRA and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE, (version 4.0) [NCI, 2009]. Summaries of the number of toxicity grades for both laboratory and non-laboratory data will be presented.

Events will be summarized by frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries will be given for all AEs, treatment-related AEs, SAEs and AEs leading to discontinuation of study treatment. AEs, if listed in the NCI-CTCAE (version 4.0) [NCI, 2009] will be summarized by the maximum grade. Otherwise, the AEs will be summarized by maximum intensity.

The incidence of deaths and the primary cause of death will be summarized.

DLTs will be listed for each subject and summarized by dose cohort according to IDSL standards.

13.7.2.3. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed on the days specified in the Time and Events Tables Section 7.1.

Hematology and clinical chemistry data will be summarized using frequencies and proportions according to NCI-CTCAE (version 4.0) [NCI, 2009]. Laboratory test results outside the reference ranges that do not have associated NCI-CTCAE criteria will be summarized at each scheduled assessment. Results will be flagged using toxicity grades, if available, or as normal or abnormal (high or low) with reference to standard reference ranges. Further details will be provided in the RAP.

13.7.2.4. Other Safety Measures

Data for vital signs, ECGs, and ECHOs will be summarized based on predetermined criteria identified to be of potential clinical importance (PCI). Vital signs will be listed for each subjects at all measured time points. A descriptive summary including change from baseline pre-dose will also be presented. Individual profiles of BP will be plotted by time. Further details will be provided in the RAP.

13.7.3. Pharmacokinetic Analyses

13.7.3.1. Pharmacokinetic Parameters

PK analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation (CPMS) Department, GSK.

PK analysis of drug concentration-time data will be conducted by non-compartmental methods and exploratory compartmental methods under the direction of CPMS, Quantitative Sciences, GSK. The following PK parameters will be determined if data permit:

- Cmax
- tmax
- area under the plasma concentration-time curve (AUC(0-t), AUC(0-τ) (repeat dosing) and/or area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-∞)] (single dose)
- apparent terminal phase elimination rate constant (λz) (single dose)
- apparent terminal phase half-life (t½) (single dose)
- apparent MRT
- population pharmacokinetic parameters including CL, Q, V, Vm and Km

13.7.3.2. Statistical Analysis of Pharmacokinetic Data

Statistical analyses of the non-compartmental PK parameters data will be the responsibility of Oncology, Clinical Statistics, GSK. Statistical analysis of the exploratory compartmental PK parameters data will be the responsibility of CPMS, Quantitative Sciences, GSK. Plasma GSK2849330 concentration-time data from dose escalation will be analyzed by non-compartmental methods with WinNonlin [Version number 5.2].

From the plasma concentration-time data, the following PK parameters will be determined, as data permit: Cmax, tmax, AUC(0-t) and AUC(0-∞), apparent terminal phase half-life (t1/2), and MRT. Trough concentration (Cτ) samples collected on the specified days will be used to assess attainment of steady state.

Plasma concentration-time data will be listed by dose and summarized using descriptive statistics (n, mean, standard deviation SD, median, minimum and maximum) by planned relative assessment time. Mean and/or median values will be plotted over time. Individual plasma and urinary (if available) PK parameters values as well as descriptive summary (mean, SD, median, minimum, maximum, geometric mean, and the standard deviation, 95% confidence interval (CI) of log-transformed parameters (if applicable) by dose cohort or group will be reported.

Cmax and AUC (AUC(0-∞), and AUC(0-τ)) will be plotted as a function of the dose administered.

Further exploratory statistical analysis of any or all the pharmacokinetic endpoints may be performed as appropriate including dose proportionality.

PK data will be presented in graphical and/or tabular form and will be summarized descriptively.

13.7.3.3. Population Pharmacokinetics

Statistical analysis of the population PK parameter data will be the responsibility of CPMS, Quantitative Sciences, GSK.

Plasma concentration-time data from the groups in Part 2 may be combined with data from dose escalation and further analyzed using a population approach. A nonlinear mixed effect model may be used to determine population PK parameters and important covariates (biomarker, or disease related covariates).

PK data will be presented in graphical and/or tabular form and will be summarized descriptively.

13.7.4. Immunogenicity Analyses

The immunogenicity assessment will include the incidence (confirmed positive results only) and titers of anti-GSK2849330 binding antibodies at any time point post baseline. Full details will be provided in the RAP.

13.7.5. Pharmacokinetic/Pharmacodynamic Analyses

Data permitting, exploratory population covariate PK/PD/biomarker analyses will be provided.

13.7.5.1. Translational Research Analyses

The results of translational research investigations will be reported *in or separately from* the main clinical study report (CSR). All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Data permitting, the results of secondary translational research objectives will be reported in the main CSR. The results of exploratory biomarker research investigations will be reported separately from the main clinical study report. Full details will be provided in a RAP.

Further details on the translational research analyses will be addressed in the RAP.

13.7.5.2. Novel Biomarker(s) Analyses

The results of these biomarker investigations may be reported separately from the main CSR. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data.

Additional exploratory analyses may be performed to further characterize the novel biomarker.

13.7.6. Pharmacogenetic Analyses

Further details on PGx analyses will be addressed in Appendix 8 and the PGx RAP.

14. STUDY CONDUCT CONSIDERATIONS

14.1. Posting of Information on Clinicaltrials.gov

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

14.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements.

The study will be conducted in accordance with ICH GCP, all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- IRB/EC review and approval of study protocol and any subsequent amendments
- Subject informed consent
- Investigator reporting requirements

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study.

14.3. Urgent Safety Measures

If an event occurs that is related to the conduct of the study or the development of the IP, and this new event is likely to affect the study of subjects, the Sponsor, and the investigator will take appropriate urgent safety measures to protect subjects against any immediate hazard.

The Sponsor will work with the investigator to ensure the IRB/EC is notified.

14.4. Quality Control (Study Monitoring)

In accordance with applicable regulations, Good Clinical Practice (GCP) and GSK procedures, the site will be contacted prior to the start of the study to review with the site

staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

14.5. Quality Assurance

To ensure compliance with ICH GCP and all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

14.6. Study and Site Closure

The end of the study will be defined as the date of the LSLV enrolled.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/EC promptly and provide the reason(s) for the suspension/termination.

GSK may also close study sites which fail to recruit subjects within a predefined timeframe, as defined within the SPM.

14.7. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

14.8. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The results summary will be posted to the GSK Clinical Study Register no later than 8 months after the final primary completion date, the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome. In addition, a manuscript will be submitted to a peer reviewed journal

for publication no later than 18 months after the LSLV. When manuscript publication in a peer-reviewed journal is not feasible, a statement will be added to the register to explain the reason for not publishing.

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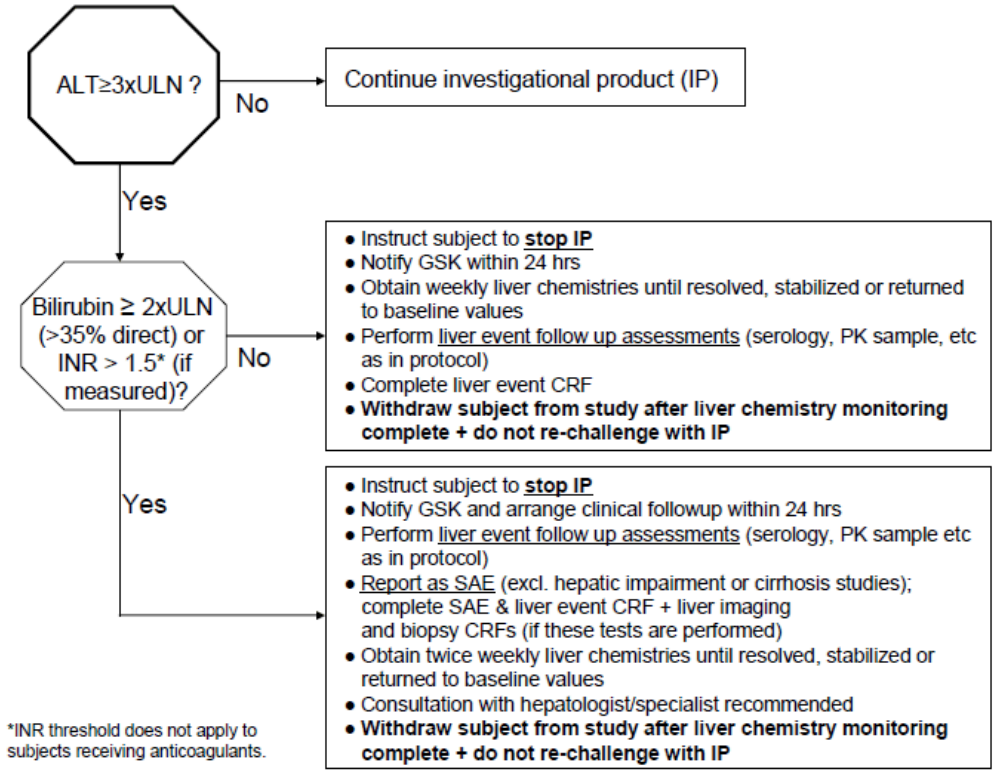
16. APPENDICES

16.1. Appendix 1: Liver Chemistry Monitoring, Interruption Stopping and Follow-up Criteria

Phase I Liver Safety Algorithm



16.2. Appendix 2: Country Specific Requirements

Specific QTc Stopping Criteria:

If specified by local requirements, a subject that meets the criteria QTc[1] below will have study treatment withheld:

The QT interval corrected for heart rate by Bazett's formula (QTcB) > 500 msec

[1]Based on average corrected QT (QTc) interval value of triplicate ECGs to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subjects should have study treatment withheld.

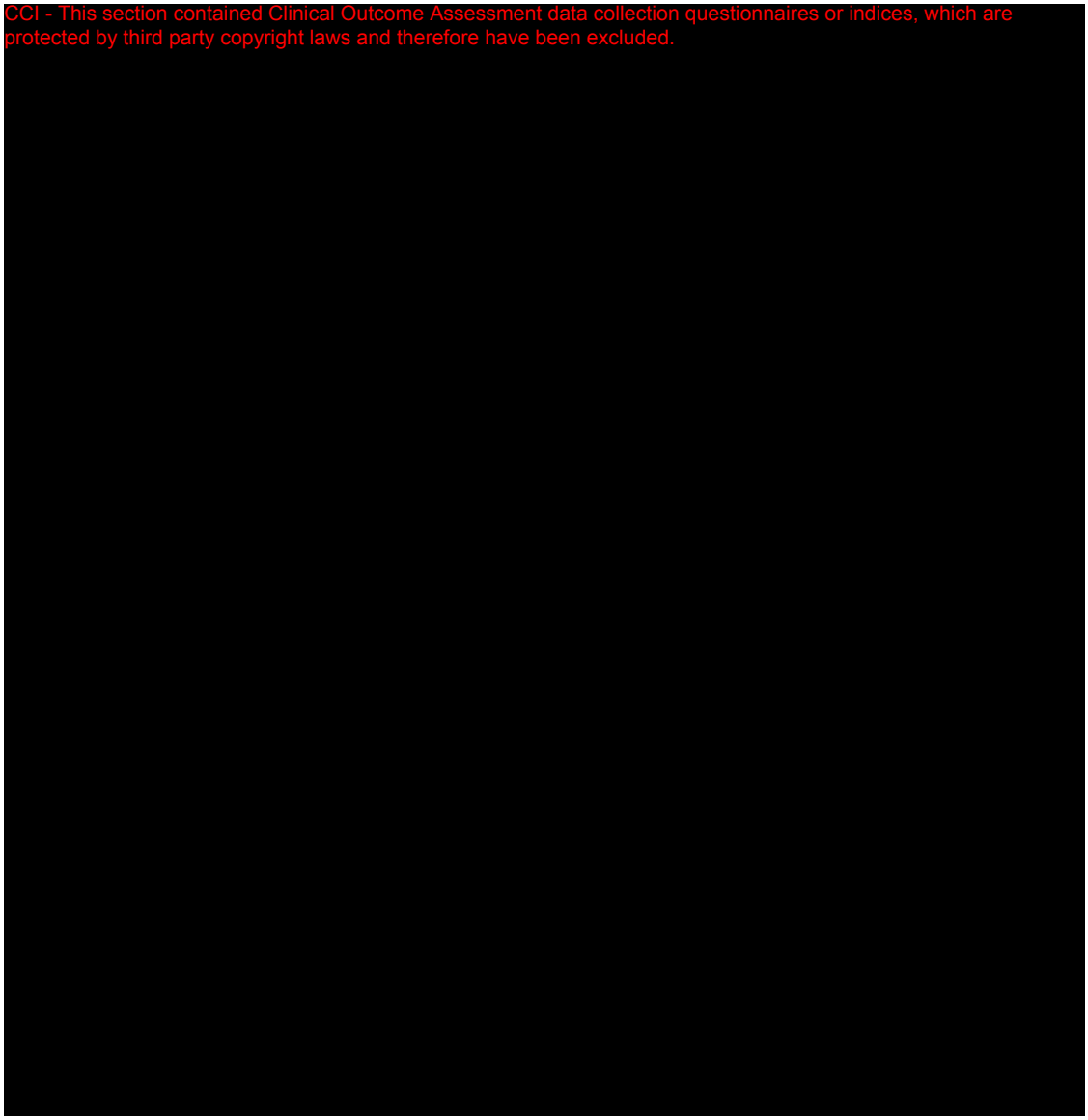
In addition, for subjects in designated countries, study treatment must be withheld for an increase in QTc >60 msec from baseline.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

No other known country specific requirements are currently required.

16.3. Appendix 3: ECOG Performance Status

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



16.4. Appendix 4: Estimated Glomerular Filtration Rate Using the Modification of Diet in Renal Disease (MDRD) Equation

Background

The Modification of Diet in Renal Disease (MDRD) equation provides an estimate of glomerular filtration rate (GFR), using values for a subject's serum creatinine, age, sex, and race (Levey, 1999).

MDRD Equation when creatinine is expressed in mg/dL:

Estimated GFR (ml/min/1.73 m^2) = 186 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if black)

MDRD Equation when creatinine is expressed in µmol/L:

Estimated GFR (ml/min/1.73 m^2) = 32788 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if black)

Reference

Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 130(6):461-70. (1999)

Glomerular Filtration Rate Interpretation

Table 16 Kidney function using GFR estimates

Stage	GFR	Equation (age in years for ≥ 18)
1	90+	Normal kidney function
2	60 - 89	Mildly reduced kidney function
3	30 - 59	Moderately reduced kidney function
4	15 - 29	Severely reduced kidney function
5	<15	Very severe, or endstage kidney failure

Website to calculate the glomerular filtration rate

http://nephron.org/MDRD_GFR.cgi

16.5. Appendix 5: RECIST 1.1 Guidelines for Evaluation of Disease

Measurable and Non-measurable Definitions

Measurable lesion:

A non nodal lesion that can be accurately measured in at least one dimension (longest dimension) of

- ≥10 mm with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (e.g., if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
- ≥10 mm caliper/ruler measurement by clinical exam or medical photography.
- ≥20 mm by chest x-ray.

Additionally lymph nodes can be considered pathologically enlarged and measurable if

- ≥15 mm in the short axis when assessed by CT or MRI (slice thickness recommended to be no more than 5 mm). At baseline and follow-up, only the short axis will be measured [Eisenhauer, 2009].

Non-measurable lesion:

All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥ 10 mm and <15 mm short axis) as well as truly non-measurable lesions, which include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques [Eisenhauer, 2009].

Measurable disease: The presence of at least one measurable lesion. Palpable lesions that are not measurable by radiologic or photographic evaluations may not be utilized as the only measurable lesion.

Non-Measurable only disease: The presence of only non-measurable lesions.
Response Criteria

Evaluation of target lesions

Definitions for assessment of response for target lesion(s) are as follows:

- CR: Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- PR: At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g., percent change from baseline).

- SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- PD: At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g., percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No target lesions at baseline.
- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

NOTE:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (e.g., sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.
- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.
- All lesions (nodal and non-nodal) should have their measurements recorded even when very small (e.g., 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.
- If a lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Evaluation of non-target lesions

Definitions for assessment of response for non-target lesions are as follows:

- CR: The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (e.g., <10 mm short axis).
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥10 mm short axis.
- PD: Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No non-target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

NOTE:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- In the presence of non-measurable only disease consideration should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.
- Sites of non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g., non-target response does not have to be "Not Evaluable").

New lesions

New malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of overall response

Table 17 presents the overall response at an individual time point for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions for subjects with measurable disease at baseline.

Table 17 Evaluation of Overall Response for Subjects with Measurable Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	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, NA= Not applicable, and NE=Not Evaluable

Table 18 presents the overall response at an individual time point for all possible combinations of tumor responses in non-target lesions with or without the appearance of new lesions for subjects with non-measurable only disease at baseline.

Table 18 Evaluation of Overall Response for Subjects with Non-Measurable Only Disease at Baseline

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non CR/Non PD	No	Non CR/Non PD
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR=complete response, PD=progressive disease, and NE=Not Evaluable

NOTE:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and will be determined programmatically by GSK based on the investigators assessment of response at each time point.

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose at a minimum interval of 8 weeks.
- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement the best response will be PD. Alternative subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria:

To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 4 weeks (28 days) after the criteria for response are first met.

References:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guidelines (version 1.1). *Eur J Cancer*. 2009; 45: 228-2.

16.6. Appendix 6: Modified irRC from RECIST 1.1

Modified immune-related response criteria (irRC)

Modified irRC is modified from RECIST 1.1 based on immune-related response criteria [Wolchok, 2009].

Measurable lesions/non-Measurable lesions

The definition of measurable lesions and non-measurable lesions are based on RECIST 1.1. [Eisenhauer, 2009]

Index lesions

All target lesions from RECIST 1.1 assessment will be referred to as index lesions in the modified irRC.

Non-index lesions

All non-target lesions from RECIST 1.1 assessment will be referred to as non-index lesions in the modified irRC.

Measurable and Non-measurable new lesions

New lesions will be classified as measurable and non-measurable lesions based on RECIST 1.1. For measurable new lesions, measurement will be recorded in CRF.

Calculation of immune-related Sum of Lesion Diameters (irSLD)

- **irSLD at baseline** is the sum of diameters for all index lesions at baseline prior to treatment on Day 1.
- **irSLD at post-baseline assessment**: at each post-baseline disease assessment, the diameters of the index lesions and of new measurable lesions are added together to provide the irSLD, see below

$$irSLD = SLD_{index} + SLD_{new,\ measurable}$$

Definition of Index Lesion Response

- **Immune-related complete response (irCR),** which is defined as complete disappearance of all index lesions. Lymph nodes that shrink to <10 mm in short axis are considered normal.
- **Immune-related partial response (irPR),** which is defined as a decrease, relative to baseline, of 30% or greater in the sum of the diameters of all index and all new measurable lesions, in the absence of irCR.

- **Note:** the appearance of new measurable lesion is factored into the irSLD, but does not automatically qualify as progressive disease until the irSLD increase by ≥20% when compared to irSLD at nadir.

- **Immune-related stable disease (irSD),** which is defined as not meeting the criteria for irCR or irPR, in the absence of immune-related progressive disease (irPD).

- **Immune-related progressive disease (irPD),** which is defined as at least a 20% increase in the sum of the diameters of all index and all new measurable lesions when compared to irSLD at nadir.

Definition of Non-index Lesion Response

- **irCR**, which is defined as complete disappearance of all non-index lesions. Lymph nodes that shrink to <10 mm short axis are considered normal.

- irPR, non-index lesions are not considered in the definition of irPR, this term does not apply.

- irSD, non-index lesions are not considered in the definition of irSD, this term does not apply.

- irPD, increase in number or size of non-index lesions does not constitute progressive disease unless/until irSLD increase by 20% compared to nadir.

Impact of New Lesions on modified irRC

New lesions alone do not qualify as progressive disease. However their contribution to total tumor burden is included in the irSLD which in turn feeds into the modified irRC for tumor response.

Definition of Overall Response using modified irRC

- **irCR**, defined as complete disappearance of all index and non-index lesions, together with no new measurable or non-measurable lesions. All lymph nodes short axes must be <10 mm. Must be confirmed no less than 4 weeks from the date of the documentation of irCR.

- **irPR**, defined as a decrease of 30% or greater in the sum of lesion diameters of all index lesions and new measurable lesions (irSLD) relative to baseline, in the absence of irCR. Must be confirmed no less than 4 weeks from the date of the documentation of irPR.

- **irSD**, defined as failure to meet the criteria for irCR or irPR, in the absence of irPD.

- **irPD,** defined as at least 20% increase in the irSLD of all index lesions and new measurable lesions over the nadir irSLD. It is highly recommended to confirm irPD no less than 4 weeks later.

Modified Immune-related overall response

Index lesion	Non-Index	New, Measurable	New, non-measurable	% change in irSLD (index and measurable new lesions)	Overall Response
irCR	irCR	Absent	Absent	100% reduction from baseline	irCR*
irCR	Non-irCR	Absent	Any	100% reduction from baseline	irPR*
irCR	Any	Absent	Present	100% reduction from baseline	irPR*
irPR	Any	Any	Any	>=30% reduction from baseline and <20% increase from nadir [2]	irPR*
irSD	Any	Any	Any	<30% reduction from baseline and <20% increase from nadir	irSD*
irPD	Any	Any	Any	>= 20% increase from nadir	irPD*#

*irCR, irPR and irPD must be confirmed no less than 4 weeks later.
Use lowest recorded tumor burden for this calculation.

References:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guidelines (version 1.1). *Eur J Cancer*. 2009; 45: 228-2.

Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009;15:7412-7420.

16.7. Appendix 7: mRECIST Criteria

Definition of Measurable and Non-measurable Disease

Measurable disease: The presence of at least one measurable lesion.

Measurable lesion:

- **RECIST 1.0**: lesions that can be accurately measured in at least one dimension, with the longest diameter (LD) being:
    - ≥20 mm with conventional techniques (medical photograph [skin or oral lesion], palpation, plain X-ray, CT, or MRI),

      OR

    - ≥10 mm with spiral CT scan.
- **mRECIST**: intrahepatic lesions that show intratumoral arterial enhancement on contrast-enhanced CT or MRI (i.e.,. viable lesions), and that can be accurately measured in at least one dimension with the longest diameter being ≥10 mm with contrast-enhanced spiral CT scan or contrast-enhanced dynamic MRI.

Non-measurable lesion: All other lesions including lesions too small to be considered measurable (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan) including bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusions, lymphangitis cutis/pulmonis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions, or disease documented by indirect evidence only (e.g*.,* by lab values). Malignant portal vein thrombosis should be considered as non-measurable lesions. Porta hepatis lymph nodes with a short axis less than 20 mm are considered reactive and not malignant.

Methods of Measurement

The same diagnostic method must be used throughout the study to evaluate a lesion.

Conventional CT and MRI: Minimum sized lesion should be twice the reconstruction interval. The minimum size of a baseline lesion may be 20 mm, provided the images are reconstructed contiguously at a minimum of 10 mm. CT is preferred, and when used, lesions must be measured in the same anatomic plane by use of the same imaging sequences on subsequent examinations. Whenever possible, the same scanner should be used.

Spiral CT: Minimum size of a baseline lesion may be 10 mm, provided the images are reconstructed contiguously at 5 mm intervals. This specification applies to the tumors of the chest, abdomen, and pelvis.

Chest X-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, MRI is preferable.

Clinical Examination: Clinically detected lesions will only be considered measurable by RECIST criteria when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography - including a ruler and subject study number in the field of view to estimate the size of the lesion is required.

Selection and Baseline Documentation of Target and Non-Target Lesions

Target Lesion Definition

'Typical' Target Lesions

Intrahepatic lesions that meet the following criteria are considered 'typical' target lesions:

- Lesions that show typical features of HCC in contrast-enhanced spiral CT or MRI studies (i.e., hypervascularity in the arterial phase with wash-out in the portal or late venous phase)
- Lesions that are measurable (as defined above)
- Lesions that are suitable for repeated measurements
- Other Target Lesions ('atypical' and extrahepatic lesions)
- 'Atypical' and extrahepatic lesions that are measurable and suitable for repeated measurements are considered target lesions

Target Lesion Selection

- The selection of target lesions will be guided initially by the presence of 'typical' intrahepatic lesions:

If 'Typical' intrahepatic lesions are present:

  - Up to 5 of these 'typical' intrahepatic lesions should be selected as target lesions at baseline. Measurement of viable tumor diameter will be applied to these lesions. All intrahepatic lesions beyond these 5 should be considered as non-target lesions.
  - In addition, up to 5 measurable, extrahepatic lesions per organ should be selected as target lesions at baseline. Measurement of longest tumor diameter will be applied to these lesions. All extrahepatic lesions beyond the up-to-10 selected target lesions should be considered as non-target lesions.

If no 'Typical' intrahepatic lesions are present:

  - In case measurable intrahepatic HCC lesions are present at baseline but do not meet the criteria for 'typical' lesions, due to atypical vascular patterns, these measurable intrahepatic lesions as well as measurable extrahepatic lesions should be assessed at baseline. Up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should

be identified as target lesions and recorded and measured. A measurement of longest diameter will be applied to these lesions.

Non-Target Lesions

- Measurable lesions other than the target lesions and all sites of non-measurable (evaluable) disease will be identified as non-target lesions. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. Non-target lesions may include:

Intrahepatic lesions:

- Not well-delineated HCC lesions including infiltrative-type and diffuse HCC
- HCC lesions with atypical contrast-agent enhancement patterns
- HCC lesions showing local recurrence after previous loco-regional treatment without meeting the criteria for 'viable' lesions (i.e., lack of clear-cut hypervascular recurrence and/or well-delineation from the surrounding liver tissue)
- Portal vein tumor invasion and/or thrombosis
- Porta hepatis lymph node(s) considered as malignant (i.e., >20 mm in the short axis)
- Intrahepatic viable lesions in excess of the 5 lesions in the liver selected as target lesions

Extrahepatic lesions:

- Extrahepatic lesions in excess of the 5 lesions per organ selected as target lesions
- Non-measurable but evaluable disease (*i.e.,* cutaneous or bone lesions, etc.)

Calculation of Sum of Target Lesions

- Documentation of indicator lesion(s) should include date of assessment, description of lesion site, dimensions, and type of diagnostic study used to follow lesion(s).
- All measurements should be taken and recorded in metric notation, using a ruler or callipers.

If 'Typical' intrahepatic lesions are present:

The sum of the viable diameters of all 'typical' intrahepatic target lesions (up to 5 lesions total) and of the longest overall diameters of extrahepatic target lesions (5 per organ) up to a maximum of 10 target lesions in total will be calculated and reported as the baseline sum. This baseline sum will be used as the reference for determining tumor response. Note the longest viable diameter may not be on the same section of liver as the longest overall diameter.

If no 'Typical' intrahepatic lesions are present:

The sum of the longest overall diameters for all target lesions up to a maximum of 10 target lesions in total will be calculated and reported as the baseline sum of the longest diameters, which will be used as reference to characterize the objective tumor response according to RECIST 1.0.

In case of an initial tumor shrinkage, the smallest sum of (1) viable diameters (for 'typical' intrahepatic lesions) or of (2) longest diameters (for 'atypical' intra- and extrahepatic lesions) recorded following baseline will be used as reference to determine disease progression.

Response Criteria

Disease assessments are to be performed every 6 weeks after initiating treatment. However, **subjects experiencing a partial or complete response must have a confirmatory disease assessment at least 28 days later.** Assessment should be performed as close to 28 days later (as scheduling allows), but no earlier than 28 days.

Definitions for assessment of response for target lesion(s) are as follows:

Complete Response (CR) – both of the following criteria must be met:

- For 'typical' intrahepatic target- and non-target lesions, complete disappearance of any intratumoral contrast-agent enhancement in the arterial phase of spiral CT or dynamic MRI

  AND

- For 'atypical' intra- and extrahepatic target- and non-target lesions, complete disappearance of all evidence of target- and non-target lesions in spiral CT or MRI

Partial Response (PR) –

- A decrease of >30% in the sum of the longest diameters of all target lesions (defined below), with the baseline sum of the longest diameters of all target lesions as reference.
- The "sum of the longest diameters of all target lesions" is defined as the sum of the following:
  - The sum of the longest viable diameters of 'typical' intrahepatic target lesions

    AND

  - The sum of the longest overall diameters of 'atypical' intra- and extrahepatic target lesions.

Stable Disease (SD) – neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD) – one or more of the following criteria must be met:

- For 'typical' intrahepatic target lesions, increase of >20% in the sum of the longest viable diameters of target lesions, taking as reference the smallest sum of viable diameters of target lesions recorded since the treatment started

  OR

- For 'atypical' intra- and extrahepatic lesions increase of >20% in the sum of the longest diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since the treatment started

  OR

- New hepatic lesion with the longest diameter of at least 10 mm with the vascular pattern characteristic for HCC, i.e., hypervascularization in the arterial phase with wash-out in the portal venous (or late venous) phase of contrast-enhanced spiral CT or MRI imaging

  OR

- New hepatic lesion larger than 10 mm without the vascular pattern characteristic for HCC, but evidence of growth of at least 10 mm in subsequent scans. Note: individual radiological events will be adjudicated retrospectively as PD at the time when it was first detected by imaging techniques, if the criteria are fulfilled (≥ 20 mm) on subsequent radiological testing

  OR

- Unequivocal progression of existing non-measurable lesions. However, any new or worsening of pre-existing effusion (ascites, pleural effusion, etc.) will not be considered progression unless there is cyto-pathological confirmation of malignancy

  OR

- Appearance of one or more new extrahepatic lesions of any size

  OR

- Unequivocal progression of existing intra- or extrahepatic non-target lesion(s)
- In the absence of clinical progression or concurrent progression in target lesions, progression of non-target lesions that is equivocal should be confirmed by a repeat evaluation at 3-6 weeks. If the progression is confirmed, the date of the first (equivocal) assessment will be taken as the date of progression

Evaluation of Overall Response for mRECIST-Based Response

The overall response is the best response recorded from the start of the treatment until disease progression/recurrence is documented. In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The following table presents the evaluation of best overall response for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation Criteria

- To be assigned a status of PR or CR, a confirmatory disease assessment should be performed no less than 28 days after the criteria for response are first met.
- To be assigned a status of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 12 weeks.

References:

Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis.* Feb 2010;30(1):52-60.

16.8. Appendix 8: Pharmacogenetics (PGx)

PGx Research

PGx – Background

PGx is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the PK (absorption, distribution, metabolism, and elimination), PD (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx analysis include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002]	HLA-B*5701	Individuals with HLA-B*5701 variant may be at increased risk for experiencing hypersensitivity to abacavir. Clinical assays are available for HLA-B*5701 but none has been validated. HLA-B*5701 screening would supplement but never replace abacavir clinical risk management strategies aimed at minimizing rare but serious outcomes associated with abacavir hypersensitivity.
Carbamazepine	Seizure, Bipolar disorders & Analgesia [Chung, 2010; Ferrell ,2008]	HLA-B*1502	Independent studies indicated that patients of East Asian ancestry who carry *HLA-B*15:02* are at higher risk of Stevens-Johnson Syndrome and toxic epidermal necrolysis. Regulators, including the US FDA and the Taiwanese TFDA, have updated the carbamazepine drug label to indicate that patients with ancestry in genetically at risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine..
Warfarin	Cardiovascular [Neergard, 2006; Wilke, 2005]	CYP2C9	SAEs experienced by some subjects on warfarin may be explained by variations in the CYP2C9 gene that influences the degree of anticoagulation achieved.

Drug	Disease	Gene	Outcome
Irinotecan	Cancer [FDA News Release, 2005]	UGT1A1	Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation, might be too high for another subject without this variation, raising the risk of certain side effects. A genetic blood test (Invader UGT1A1molecular assay) is available that can detect variations in the gene.

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

Regarding the pharmacology of GSK2849330, of specific interest are genetic polymorphisms of Fc receptors which modify affinity of the receptor(s) for binding to IgG antibodies [Hogarth, 2012]. FcγRIIIa polymorphisms have been described (Val158 or Phe158) which exhibit different affinities for IgG and consequent downstream effector cell functionality such as ADCC. Furthermore, these polymorphisms are clinically important as they have been shown to affect the efficacy of therapeutic antibodies in patients [Hogarth, 2012].

Collection of whole blood may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to GSK2849330.

PGx Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a possible genetic relationship to handling or response to GSK2849330. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK2849330 that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and the PK and/or PD of study treatment
- Relationship between genetic variants and safety and/or tolerability of study treatment
- Relationship between genetic variants and efficacy of study treatment

Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives study treatment may take part in the PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Assessments and Procedures

Blood samples can be taken for PGx assessments.

If taking blood samples: in addition to any blood samples taken for the clinical study, a whole blood sample (~10 mL) will be collected for the PGx research using a tube containing Ethylenediaminetetraacetic acid (EDTA). It is recommended that the blood sample be taken at the first opportunity after a subject has been enrolled and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labeled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of GSK2849330 has been completed and the study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to GSK2849330.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- The sample is retained for PGx research.
- Any PGx sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up to that point.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

PGx Analyses

Specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying AEs, and those linked to study disease and, thus, linked to drug response.

The candidate genes that may be investigated in this study include the following: the GSK Absorption, Distribution, Metabolism and Excretion genes. These play a central role in drug PK and PD. In addition, continuing research may identify other enzymes, transporters, proteins, or receptors that may be involved in response to GSK2849330. The genes that may code for these proteins may also be studied.

Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) located throughout the genome. This approach is often employed when potential genetic effects are not well understood.

The results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. In all cases, appropriate statistical methods will be used to analyze the genetic markers in the context of other clinical data. Statistical methods may include, but are not limited to Hardy-Weinberg Equilibrium testing, Comparison of Demographic and Baseline Characteristics by Genotype, Evaluation of Genotypic Effects, Evaluation of Treatment by Genotype and Gene-Gene Interaction, Linkage Disequilibrium, Multiple Comparison and Multiplicity and/or Power and Sample Size Considerations. Detailed description of the analyses to be conducted will be documented in the PGx RAP.

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood/saliva being taken for PGx research.

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the cumulative PGx research results in the CSR.

In general, GSK does not inform the investigator, subject or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results unless required by law. The information generated from PGx research is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research.

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16.9. Appendix 9: Management of Diarrhea

In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea (Benson, 2004). Presented in the sections below are the recommended guidelines for the management of diarrhea published by the ASCO panel (Benson, 2004).

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations such as over the counter (OTC) medications, including herbal supplements, that may be useful in the evaluation of their diarrhea history.

Definitions

National Cancer Institute (NCI) guidelines define diarrhea compared to baseline (Table 19).

Table 19 Grading of Diarrhea

Adverse Event Grade	Diarrhea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living (ADL)
4	Life-threatening consequences; urgent intervention indicated
5	Death

Uncomplicated diarrhea is considered mild-to-moderate and defined as CTCAE Grade 1 or 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as any CTCAE Grade 3 or 4 diarrhea, or Grade 1 or 2 with one or more of the following signs or symptoms:

- Moderate to severe abdominal cramping
- Nausea/vomiting ≥Grade 2
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding (red blood in stool)
- Dehydration

Management of Uncomplicated Mild to Moderate Diarrhea

Recommendation: Initial management of mild to moderate diarrhea should include dietary modifications (e.g., eliminating all lactose-containing products and high osmolar dietary supplements), and the patient should be instructed to record the number of stools and report symptoms of life-threatening sequelae (e.g., fever or dizziness on standing). Loperamide should be started at an initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg/day).

If diarrhea resolves with loperamide, the patients should be instructed to continue dietary modifications and to gradually add solid foods to their diet. In the case of chemotherapy-induced diarrhea, patients may discontinue loperamide when they have been diarrhea-free for at least 12 hours.

If mild to moderate diarrhea persists for more than 24 hours, the dose of loperamide should be increased to 2 mg every 2 hours, and oral antibiotics may be started as prophylaxis for infection.

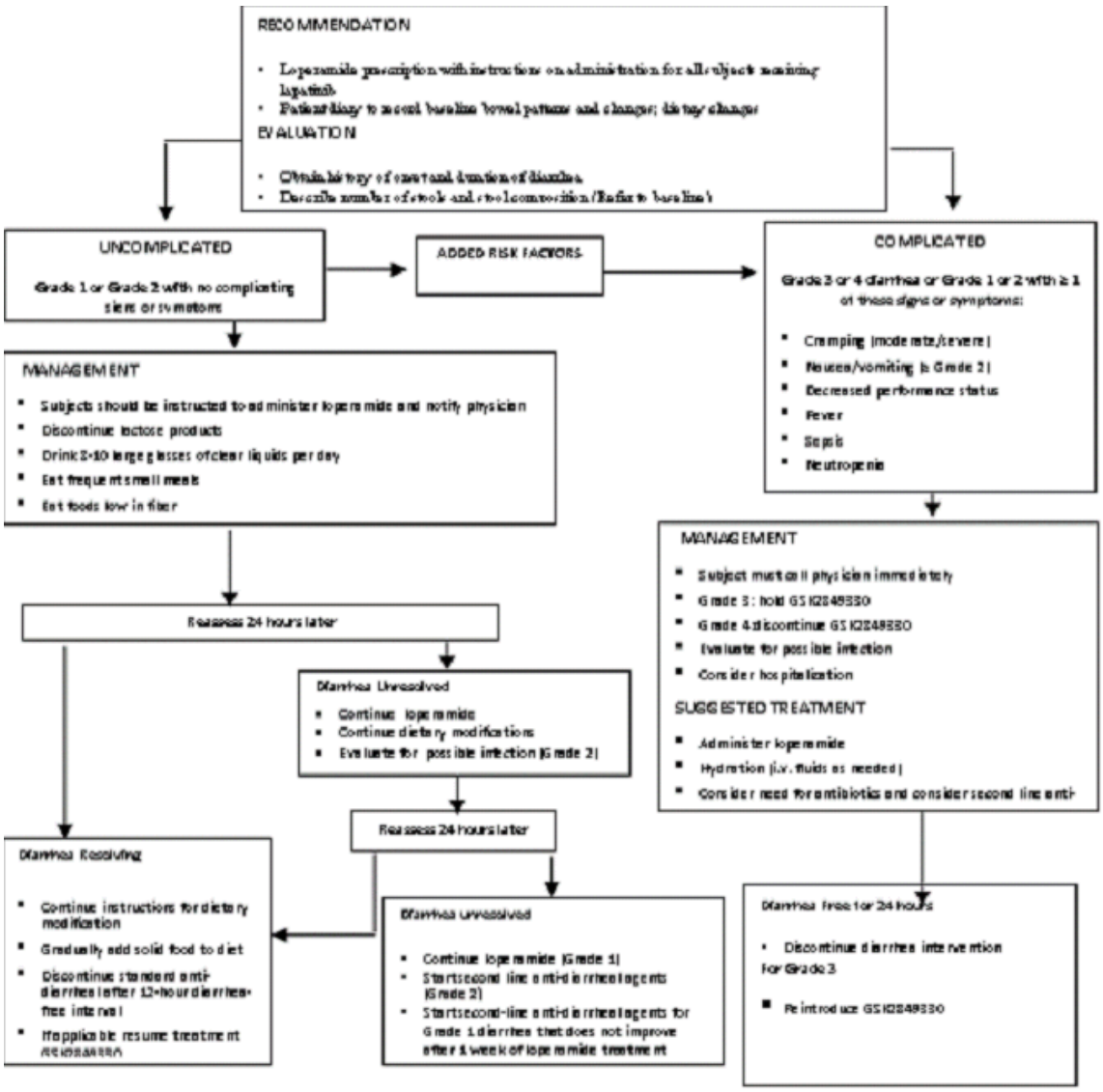
If mild to moderate chemotherapy-induced diarrhea has not resolved after 24 hours on high-dose loperamide (48 hours total treatment with loperamide), it should be discontinued and the patient should be started on a second-line antidiarrheal agent such as subcutaneous (SC) octreotide (100- to 150-μg starting dose, with dose escalation as needed) or other second-line agents (e.g., oral budesonide or tincture of opium). In the case of chemotherapy-induced diarrhea, the patient should be seen in the physician's office or outpatient center for further evaluation, including complete stool and blood work-up. Stool work-up should include evaluation for pathogens. Fluids and electrolytes should be replaced as needed.

Aggressive Management of Complicated Cases

Recommendation: Aggressive management of complicated cases should involve IV fluids; octreotide at a starting dose of 100 to 150 g SC tid or IV (25 to 50 g/h) if the patient is severely dehydrated, with dose escalation up to 500 g until diarrhea is controlled, and administration of antibiotics (e.g., fluoroquinolone). This may require admission to the hospital; for select patients, diarrhea may be managed with intensive home nursing or in a day hospital. Stool work-up (evaluation for blood, fecal leukocytes, *C. difficile*, *Salmonella*, *Escherichia coli*, *Campylobacter*, and infectious colitis), complete blood count, and electrolyte profile should be performed. This may not be appropriate for radiotherapy-induced diarrhea. Any patient with chemotherapy-induced diarrhea who progresses to Grade 3 or 4 diarrhea after 24 or 48 hours on loperamide should also be treated as described above. Continue intervention as described until the patient has been diarrhea-free for 24 hours.

These recommendations for the aggressive management of complicated cases of chemotherapy-induced diarrhea are based on evidence that the GI syndrome is an indicator that the patient may be at serious risk for dehydration and/or infection and other potentially life-threatening complications. Moreover, loperamide, even at high-doses, may be less effective in patients with Grade 3 or 4 diarrhea. Therefore, it is appropriate to start immediate octreotide therapy (either SC or IV if the patient is already severely dehydrated) along with antibiotics.

Figure 2 Algorithm for the management of diarrhea



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16.10. Appendix 10: Protocol Amendment Changes

Amendment 1

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Typographical and formatting errors have been corrected and minor clarifications have been made throughout the document. These corrections have not been listed in this appendix, unless the correction changed the context or meaning of the text.

Addition of Groups to Part 2 and Changes to Inclusion and Exclusion Criteria

Four molecularly-defined, tumor histology groups were added for study during Part 2: Group 1 will include subjects with HER3-expressing melanoma, Group 2 will include subjects with HER3-expressing gastric/gastroesophageal cancer, Group 3 will include subjects with HER3 and NRG1-expressing cancers of the head and neck, and Group 4 will include subjects with HER3 and NRG1-expressing non-small cell lung carcinoma (NSCLC).

Additional inclusion criteria for subjects in Part 2 were added to clarify the number of prior lines of therapy allowed for study entry and to require subjects to undergo pre and on-treatment tumor biopsies.

Additional tumor histology groups of subjects predicted to be sensitive to the study drug based on emerging biomarkers may be added

References to cohorts of subjects in Part 2 were removed and replaced with groups of subjects as subjects.

The exclusion criteria for subjects with untreated brain or meningeal metastases and subjects treated for stable brain metastases were clarified.

Sample Size, Power, and Stopping Rules

The approximate number of subjects in Part 1 was changed from 10 to 13, to accommodate the additional weekly cohort. The anticipated number of subjects in Part 1 is now 34.

New Cohort in Part 1

An additional cohort of subjects was added to Part 1. This cohort will receive weekly treatment with 30 mg/kg GSK2949330, with an option to reduce dosing frequency to every 2 weeks after 24 weeks.

Concomitant Medications

Permitted and prohibited medications (growth factors, anticoagulants, and corticosteroids) were clarified.

Pharmacokinetic Parameters and Sampling Times

A rationale for adding a weekly dosing regimen was added.

PK sampling times were revised for subjects in Part 1enrolled under this amendment and for subjects enrolled in Part 2.

The predicted half-life of GSK2849330 was changed from 8-9 days to 7 days at 30 mg/kg. The expected dosing frequency was changed from ≥2 weeks to 1-2 weeks.

Preliminary noncompartmental and population PK parameters for the 1.4 mg/kg, 3 mg/kg, and 10 mg/kg doses were added.

Efficacy Population

An Efficacy Population was defined.

New Nonclinical and Preclinical Findings

Recent findings on the biodistribution of GSK2849330 in mice were added.

Preclinical and nonclinical findings on HER3 antibodies from recent studies and abstracts were added, including the rationale for the tumor types selected for Part 2.

Study Completion

The definitions for subject and study completion were clarified.

Disease Assessment

The timing for disease assessment at the end of the study was clarified.

Serum Samples for Immunogenicity

The timing for serum samples for immunogenicity at the end of the study was clarified.

Management of Diarrhea and other Toxicities

The recommendations for management of diarrhea were expanded.

Infusion Reactions

The requirement for a sample for selected cytokines in subjects experiencing suspected infusion-related reactions was added.

Vials and Preparation of Investigational Product

Vials containing 5 mL of investigational product were introduced, and 1-mL vials will also continue to be used.

Safety Assessments

Clarification regarding ECHO as the preferred method of LVEF assessment has been added.

The criterion for withholding of study treatment for QTc prolongation was clarified.

List of Specific Changes

Title Page, Description

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

This is a Phase I, first time in human (FTIH), open-label, multi-center, dose-escalation study of the anti-HER3 monoclonal antibody, GSK2849330 administered to subjects with HER3-expressing **or HER3 and NRG1-expressing** solid tumors. The study will be conducted in two parts. Part 1 will include dose escalation and pharmacokinetic (PK)/ pharmacodynamic (PD) cohorts to evaluate safety, PK, and PD to guide selection of dose regimen(s) for Part 2. ~~Part 2 will include up to 3 cohorts which may include tumor type specific cohorts and/or a histology-independent cohort of subjects~~**Part 2 will include at least 4 molecularly-defined tumor histology groups that will be studied** to further characterize safety, PK, PD, and evaluate initial clinical activity of GSK2849330.

Title Page, Authors

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

PPD ~~Oncology R&D, UP, USA~~
PPD ~~Global Clinical Safety & Pharmacovigilance, USA~~
PPD ~~Biopharm R&D, Stevenage, UK~~
PPD ~~Oncology R&D, UP, USA~~
PPD **Projects Clinical Platforms and Sciences, RTP, USA**
PPD Oncology Biomarkers, UP, USA
PPD Biopharm Clinical Pharmacology~~and Biometrics~~, UM, USA
PPD ~~Global Clinical Operational Sciences, RTP, USA~~
PPD Biopharm R&D, UM, USA
PPD Global Oncology Data Sciences, RTP, USA
PPD ~~Biopharm R&D, UM, USA~~
PPD **Oncology R&D, UP, USA**
PPD Oncology Clinical Statistics, UP, USA

Sponsor Signatory

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)
~~Mark J. Cornfeld, M.D., MPH~~
Li Yan, MD, PhD

Sponsor/Medical Monitor Information Page

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Role	Name	Day Time Phone Number	After-hours Phone/Cell/ Pager Number	Fax Number	GSK Address
Primary Medical Monitor	PPD ~~MD~~ PPD **MD**	PPD PPD PPD PPD	PPD PPD PPD PPD	PPD PPD PPD PPD	1250 South Collegeville Road Mailstop ~~UP4400~~**UP4410** Collegeville, PA 19426, USA PPD PPD
Secondary Medical Monitor	PPD ~~MD~~ PPD PPD	PPD PPD PPD PPD	PPD PPD PPD PPD	PPD PPD	~~709 Swedeland Road King of Prussia, PA 19406~~ PPD **Gunnels Wood Road Stevenage Herts, SG1 2NY** PPD
Tertiary Medical Monitor	PPD **MD, PhD**	PPD PPD	PPD PPD	PPD PPD	**1250 South Collegeville Road Mailstop UP4410 Collegeville, PA 19426, USA** PPD

Protocol Synopsis, Study Rationale

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~

GSK2849330 is a humanized glycol-engineered IgG1/IgG3 mAb with enhanced Fc-effector function potency, directed against HER3 (Erb3), a signalling and drug resistance target expressed on a wide range of solid tumors. This FTIH, open-label, dose escalation study will assess the safety, PK, PD, and preliminary clinical effect of GSK2849330 in subjects with HER3-expressing **or HER3 and NRG1 expressing** solid tumors.

Protocol Synopsis, Study Objectives, Endpoints and Hypotheses

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Primary Objective Part 2:

To evaluate the safety of GSK2849330 in a larger ~~cohort~~ **population of subjects in molecularly-defined tumor histology groups** at the dose regimen(s) recommended for further exploration in Part 1.

Exploratory Objectives Part 2:

To explore relationship between pre-treatment HER3 **or HER3/NRG1** expression level**s** and clinical outcome.

Exploratory Endpoint Part 2

Progression-free survival (PFS), ORR according to immune-related response criteria (irRC) ad modified Response Evaluation Criteria in Solid Tumors (mRECIST) where applicable, and other tumor markers and measures of clinical benefit.

Protocol Synopsis, Study Design

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

This is a FTIH, open-label, dose-escalation study of GSK2849330 administered to subjects with HER3-expressing **or HER3 and NRG1 expressing** solid tumors. The study will be conducted in two parts.

Part 1 will include dose escalation and PK/PD cohorts to evaluate safety and PK and PD to guide selection of dose regimen(s) for Part 2.

The starting dose is 1.4 mg/kg, administered once-weekly, to be studied in a single patient (Cohort 1). If no DLTs are observed, dose escalation will progress to 3, 10, and 30 mg/kg, at a planned dosing frequency of every two weeks, **followed by a 30 mg/kg weekly cohort** with three subjects studied at each dose level (except 1.4 mg/kg). **In the cohort treated with 30 mg/kg/wk, the option to reduce the dosing frequency to every 2 weeks after 24 weeks of treatment may be exercised. The study team, in discussion with the investigator(s), may select lower doses or alternative schedules besides those listed above, based on emerging safety, tolerability and PK findings.**

The occurrence of any DLTs will be evaluated using a Neuenschwander-Continuous Reassessment Method (N-CRM) to provide a model-based recommendation for dose escalation decisions. Dose escalation decisions, and any modifications to the proposed nominal dose levels or interval, will be based principally on review of safety data, including the output from the N-CRM, and will be supported by review of available PK and PD data.

Once a dose escalation cohort has been filled, additional subjects may be enrolled into the PK/PD cohorts (at any dose level determined to be tolerable). Subjects in the PK/PD cohort must consent to a pre- and on-treatment biopsy, which will provide information on target engagement and tumor-based PD markers. Blood samples will be obtained to evaluate GSK2849330 PK and circulating PD markers. Safety, PK and PD data from Part 1 will be used to support the dose regimen selection for Part 2

In Part 2, ~~up to 3 cohorts which may include tumor type specific cohorts and/or a histology-independent cohort of subjects,~~**at least 4 molecularly-defined tumor histology groups** will be enrolled at the dose regimen(s) selected based on Part 1 data. The objective of Part 2 is to evaluate safety in a larger **~~cohort~~population in molecularly**

defined, tumor histology groups of subjects at the recommended dose regimen, **Part 2 will** ~~and~~ also ~~to~~ evaluate **PD markers in paired tumor biopsies and assess** preliminary evidence of clinical benefit. Selection of the tumor types for focus in Part 2 ~~will be~~**was** based on available preclinical and external data. ~~and relevant PD and initial clinical benefit information gained from Part 1~~.

Protocol Synopsis, Number of Subjects

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Part 1: Approximately ~~10~~ **13** subjects will be enrolled to complete the planned dose escalation. If DLTs are observed, additional subjects may be enrolled in dose escalation to establish the MTD or the dose for further exploration in Part 2, as guided by the N-CRM. A target ~~minimum of 9 additional subjects and a target~~ maximum of 21 subjects with evaluable pre- and on-treatment tumor biopsies will be enrolled in the PK/PD cohorts. Additional subjects may be enrolled, if warranted, to provide sufficient safety, PK, or PD data to select the recommended dose for study in Part

Part 2: A minimum of 12 and a maximum of 30 subjects will be enrolled in each ~~expansion cohort in Part 2~~ of the groups. ~~Up to 3 expansion cohorts will be studied. Futility criteria will be evaluated as data accrues; enrollment in a cohort will be halted if futility criteria conditions are met for that cohort.~~ **Futility criteria will be evaluated as data accrues, and enrollment in a group will be halted if futility criteria conditions are met for that group.**

Protocol Synopsis, Inclusion/Exclusion Criteria

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Pre-screening Inclusion Criteria for Part~~s~~ 1 ~~and 2~~

Subjects will be eligible for inclusion in pre-screening for the study (See Section 3.2) only if all of the following criteria apply:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. Performance Status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 3).
4. Sufficient archival tumor specimen is available for HER3 IHC analysis, or subject is willing to undergo a fresh tumor biopsy for HER3 IHC analysis (see Section 7.6.1.1 for details).
5. Histologically or cytologically confirmed diagnosis of one of the following solid tumor malignancies for which no standard therapeutic alternatives exist:
    - Bladder cancer
    - Breast cancer
    - Castrate-resistant prostate cancer

- Cervical cancer
- Colorectal cancer (CRC)
- Gastric cancer
- Hepatocellular carcinoma (HCC)
- Melanoma
- Non-small cell lung cancer (NSCLC)
- Ovarian cancer
- Pancreatic cancer
- Squamous cell cancers of the head and neck region **(SCCHN)(**including parotid and nasopharynx)

Pre-screening for Part 2

Subjects with either melanoma, gastric/gastroesophageal cancer, head and neck cancer, or NSCLC who appear to meet all inclusion and exclusion criteria may be pre-screened for the study provided that sufficient tumor specimen is available for analyzing HER3 by IHC or HER3 by IHC and NRG1 by RNA analysis.

Protocol Synopsis, Screening Inclusion Criteria for Parts 1 and 2, Criterion 3

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

3. **For subjects enrolled in Part 1:subjects** ~~Subjects~~ must have tumors with documented HER3 expression (2+ or 3+) on the cell surface of the invasive component of tumor (either on archival tissue or fresh tumor biopsy) using an analytically validated IHC assay by central laboratory (see Section 7.6.1.1 for details). **Subjects enrolled in Part 2 must meet inclusion criterion 9 listed below.**

Protocol Synopsis, Screening Inclusion Criteria for Parts 1 and 2, Criterion 5,

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

5. Adequate baseline organ function defined by:

SYSTEM	LABORATORY VALUES
Hematologic	
ANC	≥1.5 x 10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥75 x 10^9/L
PT/INR and PTT	≤1.3x ULN
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 X ULN
AST and ALT	≤2.5 X ULN

SYSTEM	LABORATORY VALUES
Renal	
Serum creatinine OR Estimated glomerular filtration rate or 24-hr urine creatinine clearance[a]	≤ ULN OR ≥50 mL/min
Cardiac	
LVEF	≥ 50% by ECHO or MUGA[b]

a. Estimated glomerular filtration as calculated by the Modification of Diet in Renal Disease (MDRD) equation (Appendix 4). When both a calculated and 24-hr creatinine clearance are available, the 24-hr value will be used.

b. ECHO is the preferred method. **MUGA should be performed only if evaluation by ECHO is not available.**

Protocol Synopsis, Inclusion Criteria for Part 2 ONLY

NEW TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

As listed above for Part 1, with the exception of criterion 3 which should be replaced with the following criterion 9 and the addition of criteria 10 and 11.

Criterion 9

9. **For Group 1: subjects with previously treated, unresectable stage III or IV melanoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor (either on archival tumor or fresh tumor biopsy) using an analytically validated IHC assay by central laboratory.**
    - **Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).**
        - **Subjects with BRAF V600 mutations who already received or were intolerant of prior BRAF inhibitor therapy may be included. BRAF V600 inhibitor-naïve subjects will be eligible if a BRAF inhibitor is not available to them commercially or via a clinical trial.**
        - **Subjects may be included if they had prior immune therapy, were intolerant of prior immune therapy, or if such therapy is not available to them commercially or via a clinical trial.**

For Group 2: Subjects with previously treated, unresectable stage III or IV gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor (either on archival tumor or fresh tumor biopsy) using an analytically validated IHC assay by central laboratory.

- **Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1.).**
- **Subjects with HER2 positive disease may be included if they had prior anti-HER2 therapy or were intolerant of prior anti-HER2 therapy or if such therapy is not available to them commercially or via a clinical trial.**

For Group 3: Subjects with previously treated, unresectable stage III or IV cancers of the head and neck with documented HER3 expression (≥1+) and NRG1 expression on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy) using analytically validated assays by central laboratory.

- **Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).**
- **Subjects with locoregional recurrences amenable to definite surgery or additional radiation are excluded.**

For Group 4: Subjects with previously treated, unresectable stage III or IV NSCLC with documented HER3 expression (≥1+) and NRG1 expression on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy) using analytically validated assays by central laboratory.

- **Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1.).**
- **Subjects with anaplastic lymphoma kinase (ALK) translocation who already received or were intolerant of prior anti-ALK therapy may be included.Anti-ALK therapy-naïve subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.**
- **Subjects with EGFR mutations (e.g., exon 19 deletion and exon 21 L858R) who have documented progression (based on RECIST 1.1 criteria) or who were intolerant of prior EGFR inhibitors may be included. EGFR inhibitor-naive subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.**

Additional groups of subjects predicted to be sensitive to the study drug based on biomarker (*eg*, HER3 mutations, NRG fusions) identified with preclinical or clinical data may be added based on emerging data.

Criterion 10

Subjects must have at least one measurable lesion per RECIST v1.1.

NOTE: If the only site of measurable disease has been previously irradiated, documented progression of disease and a 4-week interval since completion of radiotherapy is required.
NOTE: In subjects with ≥1 measurable lesion, a measurable lesion may be biopsied at Screening and Day 15; however that lesion must not be selected as a target lesion for disease assessment.

Criterion 11

Subjects must have disease amendable to biopsy and agree to undergo pre- and on-treatment tumor biopsies (until the participating centers receive written notification from the Sponsor that paired tumor biopsies are no longer required for any/all groups).

Protocol Synopsis, Screening Exclusion Criteria Parts 1 and 2, Criterion 1

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

1. Subjects with leptomeningeal or brain metastases or spinal cord compression.

    - **Subjects with untreated brain or meningeal metastases are not eligible (computed tomography [CT] scans are not required to rule this out unless there is a clinical suspicion of central nervous system [CNS] disease).**
    - **Subjects with treated and radiologic or clinical evidence of stable brain metastases (confirmed by 2 scans at least 4 weeks apart), with no evidence of cavitation or hemorrhage in the brain lesion are eligible providing that they are asymptomatic and do not require corticosteroids. Subjects are not permitted to receive enzyme inducing anti-epileptic drugs.**

Protocol Synopsis, Screening Exclusion Criteria Parts 1 and 2, Criterion 3

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

3. Use of an investigational anti-cancer drug within 28 days **or 5 half-lives, whichever is longer**, preceding the first dose of GSK2849330 OR chemotherapy within the last 3 weeks (6 weeks for prior nitrosourea or mitomycin C) OR any major surgery, radiotherapy, immunotherapy or any other anti-cancer therapy within the last 4 weeks **except as noted above**.

Protocol Synopsis, Screening Exclusion Criteria Parts 1 and 2, Criterion 7

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

14. History or evidence of significant cardiovascular risk including any of the following:
    - LVEF<50%
    - A QT interval corrected for HR ~~using Fredericia's formula~~ (QTc~~F~~) ≥480 msec (≥500 msec for subjects with bundle branch block)
    - History or evidence of current clinically significant uncontrolled arrhythmias.

      Exception: Subjects with controlled atrial fibrillation for >30 days prior to enrollment are eligible.
    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment.
    - History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).

Protocol Synopsis, Pharmacokinetic/Pharmacodynamic Assessments

REVISED TEXT (new text bold and underlined, deleted text in ~~strikethrough~~)

For all subjects in the dose escalation cohorts in Part 1, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour and 6 hours after the end of infusion and at Day 8, Day 15, and Day 29 after the first dose of GSK2849330. If a subject's duration of infusion is 3 hours or longer, the 6 hour time point is optional. On days of dosing, the sample will be drawn pre-dose. Additionally the first subject in Cohort 1 will have PK samples taken at 24 hours (Day 2) and 72 hours (Day 4) after the end of infusion.

For cohorts enrolled under Amendment 1 of this protocol, more frequent PK samples will be collected including: On Day 1 pre-dose, 1 hour, 6 hours and 24 hours after the end of infusion. Pre-dose samples will be collected on Day 4, Day 8 and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85, and every 12 weeks thereafter.

For all subjects in the Part 1 PK/PD cohorts, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1 pre-dose, **and at 1 hour, 6 hours and 24 hours after the end of infusion. Pre-dose samples will be collected on Day 4, Day 8 and weekly through Day 57 with additional 1 hour post-dose samples collected on Days 28 and 57. Pre-dose samples will also be collected on Day 71, Day 85, and every 12 weeks thereafter.** ~~and 1 hr and 6 hr after the end of infusion and at 24 hr (Day 2), 72 hr (day 4), and 168 hr (Day 8) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hr time point is optional. Additional PK samples will be drawn pre-dose on Days 22 and 43 (after the first dose) for subjects on an every 3 week dosing schedule or pre-dose on Days 15 and 29 (after the first dose) for subjects on an every 2 week dosing schedule.~~

If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional.

For the ~~expansion cohorts~~ **subjects enrolled** in Part 2, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour after the end of infusion; **and pre-dose on Day 15, Day 29, day 43, Day 57, Day 85, and every 12 weeks thereafter.** ~~with an additional PK sample pre-dose on Days 22 and 43 (after the first dose) for subjects on an every 3 week dosing schedule or pre-dose on Days 15 and 29 (after the first dose) for subjects on an every 2 week dosing schedule~~.

For all subjects in Part 1 and Part 2, ~~additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and~~ if treatment continues ~~after~~ **beyond** 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken 45 days or 5 half lives (whichever is longer) after the last dose of study treatment. **Unless stated otherwise, on**~~On~~ days of dosing, **PK** sample**s** will be drawn pre-dose.

Blood samples will also be collected pre-dose, during treatment, and at disease progression to explore circulating markers of PD activity according to the schedule outlined in the Time and Events Tables (Section 7.1).

Samples for immunogenicity assessment will be obtained according to the schedule outlined in the Time and Events Tables (Section 7.1).

Protocol Synopsis, Statistical Methods

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The total number of subjects in the Part 1 dose escalation will depend on the number of dose escalations needed, but the minimum number of subjects anticipated to complete dose escalation is ~~10~~**13**. A target ~~minimum of 9 additional subjects and a target~~ maximum of 21 additional subjects with evaluable pre- and on-treatment tumor biopsies ~~will~~**may** be enrolled in the PK/PD cohorts. Cohort size is based on feasibility and the objective to provide an initial characterization of safety and PK/PD information that will inform dose regimen selection for Part 2.

In Part 2, at least 12 and up to 30-subjects will be enrolled in each ~~expansion cohort~~**group**. Each ~~cohort~~**group** ~~in Part 2~~ will include a futility analysis, whereby no additional subjects will be enrolled in a ~~cohort~~ **group** if futility criteria are met, as defined in Section 13.6.2.

The null hypothesis is:

H_0: $p \leq 10\%$

The alternative hypothesis is:

H_0: $p \geq 30\%$

Starting with a ~~cohort~~**group** of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.15 and 94 % power. ~~Cohort~~**Group** enrollment ~~is~~ **will be** stopped early for futility if the predictive probability of success is less than 6 %.The Bayesian Prior was Beta (0.2, 0.8), a weak prior with a mean response rate of 20%. The ~~cohort~~**group** outcome will be declared successful if the posterior probability of (P>0.10 observed data) is ≥ 80%.

Under the null hypothesis, the expected sample size is 20 subjects and the probability of early termination is 77 %. Under the alternative hypothesis, the expected sample size is 29 subjects and the probability of early termination is 5 %.

The All Treated Population is defined as all subjects who receive at least one dose of GSK2849330. Safety ~~and clinical activity~~ will be evaluated based on this analysis population.

The Efficacy Population will consist of all subjects from the All Treated Population for whom at least one post-dose tumor assessment by CT scan has been performed.

The **PK Population** will consist of all subjects from the All Treated Population for whom at least one post-dose PK sample is obtained and analyzed.

Additional details of the statistical analysis plan will be provided in the reporting and analysis plan (RAP).

Section 1.2.1, 1st paragraph

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An overview of the pre-clinical studies of GSK2849330 is provided below. Detailed information concerning the biology, pharmacology, pharmacokinetics (PK), and safety can be found in the Investigators' Brochure (IB) [GlaxoSmithKline Document number 2013N168399_**01**].

GSK2849330 is a humanized IgG1/IgG3 monoclonal antibody (mAb) with a molecular mass of approximately 145 kDa. GSK2849330 selectively binds HER3 at Domain III which resides in the extracellular domain (ECD) of the protein. HER3 sequences are 99% identical (99% homologous) between human and cynomolgus monkey, and 91% identical (94% homologous) between human and rat or mouse. The binding affinity of GSK2849330 for HER3 across these species is comparable: human: 2.1 nM; cynomolgus monkey: 1.7 nM; mouse: 4.1 nM; rat: 3.4 nM.In addition to directly blocking **the heregulin (NRG1)** ligand ~~(heregulin)~~ binding to the HER3 ECD, the antibody also sterically prevents the receptor from adopting the extended conformation that is required for dimerization, a prerequisite for receptor activation.

Section 1.2.3, Title

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~~Preclinical~~**Nonclinical** Safety of GSK2849330

Section 1.2.4.1

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GSK2849330 is a potent antagonist of HER3 signaling as evidenced by its ability to inhibit ~~heregulin~~**NRG1**-induced HER3 receptor phosphorylation in various ~~tumor~~ **cancer** cell lines (half maximal inhibitory concentration [IC_{50}] 2.5-30 ng/mL [17.2-207 pM]), and ~~heregulin~~**NRG1**-induced AKT phosphorylation in BxPC3 pancreatic ~~tumor cells~~ **cancer cell lines** (IC50 11 ng/mL [76 pM]). GSK2849330 is also able to inhibit **NRG1**-induced proliferation of BxPC3 cells in a concentration dependent manner (33% inhibition at 10 μg/mL [69 nM]).

ADCC assays using both high- and low-expressing HER3 human target cells demonstrated the increased potency and target cytotoxicity achieved with the ADCC-enhanced GSK2849330 compared to the WT parental antibody. For example, when **a** CHL-1 human melanoma ~~cells were~~ **cell line was** used as target cells and human peripheral blood leukocytes (PBLs) as effector cells, the potency of GSK2849330 was 245-764 pg/mL (1.7-5.3 pM) versus 35 ng/mL (241 pM) for the WT antibody. The efficacy of GSK2849330 was also tested against cynomolgus HER3 (transduced into human HEK293 cells) in combination with cynomolgus PBLs as effector cells. In this assay, GSK2849330 had IC_{50}=454-910 pg/mL (3.76-7.5 pM) whereas parental WT antibody had IC_{50}=4.2-5.5 ng/mL (29-38 pM).

GSK2849330 caused concentration-dependent complement-mediated cell lysis of HEK293 cells transduced with ~~BacMam expressing~~ full length human HER3. CDC activity level was proportional to HER3 protein expression on the cell surface, suggesting threshold HER3 expression amounts may be required to engage effective CDC activity. The level of ADCC killing may also be related to the amount of HER3 expression on the cell membrane [Bossenmaier, 2012].

Section 1.2.4.2 Studies *in vivo*

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GSK2849330 or variants have been evaluated for anti-tumor activity in **melanoma and pancreatic cancer cell line xenograft tumor** ~~a variety of tumor engraftment~~ models ~~including melanoma, pancreatic and gastric cancer. For example, twice~~ **Twice** weekly IP dosing with GSK2849330 at 0.5 to 50 mg/kg/dose, resulted in dose-dependent and statistically significant decreases ($p<0.001$ at ≥5 mg/kg) in tumor growth rates in a human melanoma cell line (~~HER3+~~CHL-1) subcutaneous xenograft model. ~~These studies were carried out in immune-compromised, CB17 SCID mice which lack T and B cells and in which advanced xenografts (~200 mm^3) had been allowed to establish.~~ Significant inhibition of tumor growth was also observed in subcutaneous ~~and orthotopic~~ pancreatic (~~HER3+~~ BxPC3) **cancer** cell line xenograft models and in a syngeneic mouse melanoma (lung colonization) model. ~~A more limited effect on tumor growth was observed in a HER2 amplified gastric cancer cell line (NCI-N87) tumor xenograft model with HER3 mAb monotherapy. Because~~ **Since xenograft studies were carried out in immune-compromised CB17 SCID mice, which lack T and B cells, and** the disposition and nature of Fcγ receptor subtypes in mouse are different to that observed in human [Smith,

2012], the effects of GSK2849330 on tumor growth in these mouse models are expected to result mainly from HER3 signaling inhibition (*eg*, ligand blocking/inhibition of heterodimerization) rather than an effect of the other potential (cell killing) modes of action for GSK2849330. ~~Indeed, similar effects on inhibition of CHL-1 tumor xenograft growth in this model were observed with a wild-type and an Fc-disabled variant of GSK2849330.~~ **In agreement with this hypothesis, GSK2849330 and Fc-disabled variant of GSK2849330 showed similar tumor growth inhibition in CHL-1 tumor xenograft**.

Section 1.3 HER3 Antibodies in Clinical Trials

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Although this is the FTIH study for GSK2849330, there is relevant experience for targeted inhibition of HER3 in cancer subjects. Initial clinical data from Phase I studies of ~~three~~**other** monoclonal antibodies targeting HER3 have been reported. Two of the antibodies, MM-121 and U3-1287, are non-enhanced human or humanized IgG1 antibodies. One antibody, RG7116, is a glycoengineered humanized IgG1 antibody reported to have enhanced potency for ADCC activity. **Another antibody, LJM716, is a fully human monoclonal antibody that inhibits both ligand-dependent and -independent activation of HER3**. These antibodies have been administered in clinical trials at doses up to 40 mg/kg ~~(loading dose) + 20 mg/kg~~ weekly IV without dose limiting toxicities (DLTs) and without reaching a maximum tolerated dose (MTD). ~~These therapies have been well-tolerated~~. The majority of adverse events (AEs) have been Grade 1 or 2 with GI toxicity and fatigue predominating across studies. Infusion reactions, although seen, were reportedly not severe [Arnedos, 2013 Lorusso, 2013, Meulendijks, 2013, Denlinger, 2011, Reynolds 2014].

Section 2.1, Part 1: Dose Escalation and PK-PD Cohorts-Exploratory Endpoint

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Objective	Endpoint
Primary	
• To determine the safety and tolerability of GSK2849330 in subjects with advanced HER3-positive solid tumors.	• AEs, serious adverse events (SAEs), DLTs, and changes in laboratory values, electrocardiograms (ECGs), and vital signs.
Secondary	
• To characterize the PK of GSK2849330 following IV administration.	• PK parameter values for GSK2849330.
• To evaluate preliminary evidence of target engagement and PD effects of GSK2849330.	• Total and phospho-HER3 from tumor tissue.
• To determine the recommended dose regimen(s) of GSK2849330 for further exploration in Part 2.	• Safety, tolerability, PK, and available PD data.
• To evaluate the immunogenicity of GSK2849330 following IV administration.	• Antibodies to GSK2849330 assessed in serum.
Exploratory	
• To further evaluate preliminary evidence of target engagement and PD effects of GSK2849330.	• Pre- and post- treatment biomarkers (cells, proteins, ribonucleic acid [RNA] and/or deoxyribonucleic acid [DNA]) from circulation, skin, and/or tumor tissue.
• To explore relationships between GSK2849330 PK, markers of target engagement, and /or PD markers.	• GSK2849330 concentration-time profile and PK parameters, target engagement and PD markers in circulation, skin, and/or tumor.
• To explore preliminary clinical tumor outcomes after treatment with GSK2849330.	• Preliminary evidence of clinical benefit as assessed by overall response rate (ORR), tumor markers, and other measures of clinical benefit
Pharmacogenetic (PGx) Exploratory	
• To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.	• Genetic variations in selected candidate genes, such as the FCγ receptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.

Section 2.2, Title

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Part 2: ~~Expansion Cohorts~~**Molecularly-Defined Tumor Histology Groups**

Objective	Endpoint
Primary	
• To evaluate the safety of GSK2849330 in a larger ~~cohort~~ **population of subjects in molecularly-defined tumor histology groups** at the dose regimen(s) recommended for further exploration in Part 1.	• AEs, SAEs, DLTs, and changes in laboratory values, ECGs, and vital signs.
Secondary	
• To evaluate preliminary evidence of clinical benefit.	• ORR, tumor markers, and other measures of clinical benefit.
• To further characterize target engagement and PD effects of GSK2849330.	• Total and phospho-HER3 from tumor tissue.
• To further characterize the PK of GSK2849330.	• PK parameter values for GSK2849330
• To characterize the relationship between GSK2849330 PK, markers of target engagement, and/or PD markers.	
• To evaluate the immunogenicity of GSK2849330 following IV administration.	• Antibodies to GSK2849330 in serum
Exploratory	
• To explore additional measures of clinical benefit.	• Progression free survival (PFS), ORR according to immune-related response criteria (irRc) and modified Response Evaluation Criteria in Solid Tumors mRECIST where applicable, and other tumor markers and measures of clinical benefit
• To further characterize target engagement and PD effects of GSK2849330.	• Pre- and post- treatment biomarkers (cells, proteins, RNA and/or DNA) from circulation, ~~skin, and~~/or tumor tissue.
• To explore relationship between pre-treatment HER3 **and NRG1**expression levels and clinical outcome.	• Pre-treatment HER3 and NRG1 expression levels, efficacy outcome parameters.

Objective	Endpoint
• To identify molecular features potentially predictive of response to GSK2849330.	• Prediction analysis of biomarkers (cells, DNA, RNA or protein) in tumor,~~skin,~~ and/or circulation with efficacy endpoints.
Pharmacogenetic (PGx) Exploratory	
• To investigate the relationship between genetic variants in candidate genes and safety, tolerability, PK, PD, and/or efficacy of GSK2849330.	• Genetic variations in selected candidate genes, such as the FCγ receptor family, safety, tolerability, PK, PD, and/or efficacy endpoints.

Section 3.1 Discussion of Study Design

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Protocol waivers or exemptions are not allowed. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Section 7.1) are essential.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

This is a Phase I, FTIH, open-label, multi-center, dose-escalation study of the anti-HER3 antibody, GSK2849330, in subjects with advanced solid tumors expressing HER3 (see Inclusion Criteria 3 **and 9**). The study will be conducted in two parts as depicted below.

Part 1
Dose Escalation Cohorts
To determine the safety, tolerability, PK and preliminary PD of GSK2849330, in support of selection of the recommended dose(s) and regimen(s) for further exploration in subjects with advanced solid tumors with HER3 expression

PK/PD Cohorts

Subjects that agree to give pre- and on- treatment tumor biopsies will be enrolled in the PK/PD cohorts to support selection of the recommended dose(s) and regimen(s) for Part 2. Up to 3 subjects with evaluable pre- and on-treatment tumor biopsies will be enrolled at each dose level after that dose is determined tolerable.

↓

Part 2
~~Expansion Cohort~~ Molecularly-Defined Tumor Histology Groups
To determine safety and preliminary evidence of clinical benefit of GSK2849330, and to further evaluate the PK and PD of GSK2849330 at the recommended Part 2 dose(s) and regimen(s) in subjects with selected HER3 **or HER3 and NRG1** expressing tumor types.

Section 3.2 Pre-Screening

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Subjects will be required to undergo pre-screening to determine if their tumor is HER3 expressing **or HER3 and NRG1 expressing** (~~2+ or 3+ by IHC;~~ details regarding HER3 **and NRG1** expression requirements will be described in the SPM). Subjects with study eligible advanced solid tumors ~~(see Pre-Screening Inclusion Criteria 5)~~will sign a separate Informed Consent Form (ICF) to allow for pre-screening of archival tumor or tissue from fresh tumor biopsies for HER3 expression by IHC **or for HER3 by IHC and NRG1 expression by quantitative real-time reverse transcription polymerase chain reaction (qRT-PCR) assay**.

Section 3.3 Part 1: Dose-Escalation Phase, 3rd paragraph

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Starting with Cohort 2, the dose escalation will continue using the Neuenschwander-continuous reassessment method (N-CRM) [Neuenschwander, 2008] with 3 subjects in each cohort as described below.After the first subject is dosed in Cohort~~s~~ 2 ~~through 4,~~**and all subsequent cohorts**, the second and third subjects will not be dosed until the first subject has been observed for at least 24 hours for evidence of unanticipated acute toxicity.

Section 3.3 Part 1: Dose-Escalation Phase, Dose Recommendation

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Dose recommendation: Dose recommendation output from the N-CRM model will be based on the posterior probabilities that the DLT rate for each escalation dose lies in one of the following categories:

- [0%,16%) range of minimal toxicity
- [16%, 33%) range of acceptable toxicity
- [33%, 60%) range of excessive toxicity
- [60%, 100%) range of unacceptable toxicity

After each cohort, a recommendation will be made to either: 1) escalate to the next dose or regimen, 2) de-escalate, 3) recruit more subjects at the current dose, or 4) stop. The recommended dose will be the one with the highest probability of having a DLT rate in the acceptable toxicity range [16%, 33%), subject to the constraint that no dose may be skipped during dose escalation. The recommended dose has an additional requirement that the sum of the posterior probabilities of the DLT rate lying in the excessive toxicity or unacceptable toxicity range must be less than 25%. Additional subjects may also be enrolled at any specified dose level to further characterize the safety, as with traditional dose-escalation methods.

Prior to dose escalation/de-escalation, a meeting will be convened to discuss available safety, and the recommendation from the N-CRM model. The data will be reviewed by the investigator(s) and GSK study team which may include the Medical Monitor, statistician, and pharmacokineticist. The dose escalation rationale and decision for the subsequent cohort will be documented in writing with copies maintained at each site and in the GSK study files.

~~The final recommended Part 2 dose regimen(s) will be based on an overall assessment of safety taking into consideration all available data including PK, PD, and the recommendation from the N-CRM model.~~

~~Table 2 Dose Levels~~

~~Dose Level~~	**~~Dose~~**	**~~N Dose Escalation Cohorts~~**	**~~N[a] PK-PD Cohorts~~**
~~1~~	~~1.4 mg/kg weekly~~	~~1 (minimum)~~	~~up to 3~~
~~2~~	~~3 mg/kg every 2 weeks~~	~~3 (minimum)~~	~~up to 3~~
~~3~~	~~10 mg/kg every 2 weeks~~	~~3 (minimum)~~	~~up to 3~~
~~4~~	~~30 mg/kg every 2 weeks~~	~~3 (minimum)~~	~~up to 3~~
~~5 (Optional)~~	~~Lower dose and/or extended interval~~	~~NA~~	~~up to 3~~
~~6 (Optional)~~	~~Lower dose and/or extended interval~~	~~NA~~	~~up to 3~~
~~7 (Optional)~~	~~Lower dose and/or extended interval~~	~~NA~~	~~up to 3~~

~~a) A sufficient number of subjects will be enrolled in the PK/PD cohorts to obtain up to 3 evaluable pre- and on-treatment biopsy pairs per dose level (see the SPM for additional details).~~

The initial dose levels to be evaluated are outlined in Section 3.6.3.

Additional subjects may also be enrolled at any specified dose level to further characterize safety. Additional doses and schedules and loading doses may be explored, **following the rules outlined for dose escalation**, based on emerging safety, PK and PD data. following the rules outlined for dose escalation. ~~Subjects enrolled in the PK/PD cohorts will have assessments as required below and detailed in the PK/PD cohort Time and Events Table 6 and Table 7 (see Section 7.1).~~

PK/PD cohort(s): Once a given dose escalation cohort is filled, additional subjects may be enrolled into a PK/PD cohort (at any dose level determined to be tolerable) to allow for the collection of data on the PD effects of GSK2849330 as well as additional PK data.

~~All subjects in cohorts 5 through 7, as depicted in Table 2, must be enrolled in the PK/PD cohorts.~~

Subjects enrolled in the PK/PD cohorts must meet all of the relevant inclusion and exclusion criteria, have disease that is amenable to biopsy, and also agree to have pre- and on-treatment biopsies in addition to the other study procedures. Subjects will be enrolled in PK/PD cohorts in order to obtain ~~up to 3~~ evaluable pre- and on-treatment biopsy pairs per dose level (see SPM for additional details). Subjects who do not agree to, or who are unable to provide pre- and on-treatment biopsies in the PD expansion may be enrolled in dose escalation cohorts in Part 1 as they become available.

Subjects enrolled in the PK/PD cohorts may have their dose escalated to a higher completed dose level (not exceeding the MTD) once the necessary PK/PD procedures have been completed and once other criteria for intra-subject dose-escalation have been met (see Section 3.5). See the PK/PD cohorts Time and Events (~~Table 6 and Table 7~~ Table 9, Table 10) for study assessments specific to the PK/PD cohorts.

The final recommended Part 2 dose regimen(s) will be based on an overall assessment of safety taking into consideration all available data including PK, PD, and the recommendation from the N-CRM model

Section 3.4, Title

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Part 2:~~Expansion Cohort~~**Molecularly-Defined Tumor Histology Groups**

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Part 2 can begin once the recommended dose and schedule is identified in Part 1. It is possible that more than one dose and/or schedule will be evaluated in Part 2 if available PK, PD and safety data suggest that multiple doses and schedules have desirable biologic activity or if an MTD cannot be established

The selected dose level(s) will be evaluated in Part 2 for confirmation of safety and tolerability, as well as preliminary assessment of clinical benefit, in ~~one or more expansion cohorts~~ at **least 4 molecularly-defined tumor histology groups** of subjects with HER3 **or HER3 and NRG1** expressing tumors ~~(see Inclusions Criteria 3). The expansion cohorts may include tumor type specific cohorts, and/or a histology-independent cohort of subjects with any of the following tumor types: castrate-resistant prostate cancer, melanoma, CRC, non-small cell lung cancer (NSCLC), cervical cancer, squamous cancers of the head and neck region (including parotid and nasopharynx), ovarian cancer, breast cancer, bladder cancer, gastric cancer, pancreatic cancer, and hepatocellular carcinoma (HCC). All subjects must have archival tissue available for HER3 testing, or be willing to undergo a tumor biopsy to provide a sample for HER3 testing.~~ **Group 1 will include subjects with HER3-expressing melanoma. Group 2 will include subjects with HER3-expressing gastric cancer. Group 3 will include subjects with HER3 expressing and NRG1-expressing cancers of the head and neck. Group 4 will include subjects with HER3 expressing and NRG1-expressing NSCLC.**

All subjects must have archival tissue available for HER3 and if required NRG1 testing or be willing to undergo a tumor biopsy to provide a sample for testing.

~~Subjects will be enrolled in up to 3 expansion cohorts. The first 2 expansion cohorts may be opened in parallel. The third may only be opened if futility is not established in both of the first 2 expansion cohorts. Expansion cohorts will initially enroll 12 subjects with the option of expanding to a maximum of 30 subjects if futility criteria are not met using the methodology of [Lee, 2008] (See Section 13.2.2 and Section 13.6.2 for additional details). Response will be defined either as Complete Response (CR) or Partial Response (PR) as per RECIST 1.1 guidelines.~~

~~A sufficient number of subjects with disease amenable to biopsy will be enrolled to facilitate obtaining a minimum of 9 evaluable pre- and on-treatment biopsy pairs in each of the expansion cohorts.~~

Each group will initially enroll 12 subjects with the option of expanding to a maximum of 30 subjects if futility criteria are not met using well established methodology of [Lee, 2008] (See Section 13.2.2 and Section 13.6.2 for additional details).

Subjects will be required to have disease amenable to biopsy and agree to pre-and on-treatment tumor biopsies. Pre-and on-treatment biopsies are mandatory for all subjects in all groups. GSK will closely monitor and evaluate the collection of evaluable biopsies and will notify the participating centers of any change to the collection requirements for any or all groups.

Section 3.5 Intra-subject Dose Escalation

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A subject's dose level may be increased up to the highest dose level that has previously been confirmed by the investigator and GSK medical monitor as not exceeding the MTD Intra-subject dose escalations will be allowed **in both Part 1 and Part 2 (if multiple doses/regimens demonstrate a better PK profile or clinical activity)** provided that the subject has completed at least 1 post-baseline efficacy assessment without toxicity greater than Grade 2 or the occurrence of significant AEs, and prior approval has been obtained from a GSK medical monitor. Subjects will be permitted to increase dose levels multiple times provided the above criteria are met. Any dose escalations must be agreed upon by the investigator and GSK medical monitor, and must be documented on a dose escalation decision form (see the SPM) with copies maintained at the site and in the study files.

Section 3.6.1 Rationale for Study

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

HER3 expression is seen across a wide variety of solid malignancies and is associated with poor prognosis. Up-regulation of HER3 expression and activity is also associated with resistance to multiple pathway inhibitors. GSK2849330, a monoclonal antibody targeting HER3, is a new agent for subjects whose tumors express HER3 **and/or its**

ligand, NRG1. GSK2849330 ~~possesses~~ **has a unique pharmacologic profile compared to other HER2 antibodies** with multiple ~~potential~~ modes of action including inhibition of tumor signaling and increased potential for direct cell killing via enhanced ADCC and CDC activities. ~~GSK2849330 has a unique pharmacologic profile compared to non-enhanced HER3 antibody based therapies and small molecule inhibitors of HER3~~ (See Section 1.2.1 for details).

There is considerable unmet medical need across these tumor types where high HER3 expression is seen. The purpose of the dose escalation is to evaluate safety, PK, and initial PD of the drug in subjects with HER3 expressing tumors. Following dose escalation in Part 1, at least 4 molecularly defined tumor histology groups will be enrolled in Part 2. Preliminary clinical activity, biomarkers of target engagement, downstream signalling, ADCC, and CDC will be evaluated.

Section 3.6.2 Rationale for Population

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Subjects will be selected on the basis of HER3 expression on the cell membrane of the ~~invasive component of~~ tumor because **higher levels of target expression on the cell surface is required for ADCC, CDC and signaling inhibition functions of the antibody. High ,** ~~irrespective of the mechanism(s) by which clinical benefit may be achieved, target expression is an absolute pre-requisite for antibody engagement.~~ HER3 expression has been demonstrated in ~~up to two-thirds of~~ the tumor histologies being considered for this trial [Ocana, 201**3**].

Study eligibility for Part 1 is based on HER3 protein expression using an analytically validated IHC assay. For some groups in Part 2, study eligibility is further defined by NRG1 expression.

~~HER3 expression for study eligibility is defined by an IHC score of 2+ or 3+ as this is expected to provide the optimal expression levels at which clinical efficacy and PD effect will be observed based on preclinical data (refer to Section 1.2.4).~~ **HER3 is expressed in a broad range of solid tumors, including melanoma, gastric cancer, NSCLC, and squamous cell carcinoma of the head and neck (SCCHN). Upon ligand binding, HER3 heterodimerizes with other members of the HER family and acts as a mediator of drug resistance to various cancer therapies [Amin, 2010]. Phosphorylation of intracellular sites of HER3 leads to activation of PI-3K/AKT and MEK/MAPK and JAK/STAT signaling. GSK2849330 has demonstrated inhibition of HER3 activity and tumor growth in mouse xenograft models.**

For Part 2 of the study, 4 tumor types were selected for inclusion: 2 tumor types with high levels of HER3 expression (melanoma and gastric cancer) and 2 tumor types with high levels of NRG1 (ligand for HER3) expression (head and neck cancers and NSCLC).

Melanoma

In melanoma, overexpression of HER3 is associated with advanced disease and decreased survival [Reschke, 2008; Ueno, 2008]. Treatment of melanoma is underexplored in the development of HER3 inhibitors.

In CHL-1, BRAF wild-type melanoma cell line mouse xenograft model GSK2849330 treatment decreased phospho-HER3, total HER3, phospho-AKT and tumor growth.

HER3 inhibition restored the sensitivity of trametinib and dabrafenib (MEK and BRAF inhibitors, respectively) in NRG1-treated BRAF mutant melanoma cell lines.

Gastric cancer

Both HER2 and HER3 expression are probable prognostic markers in patients with gastric cancer [Park, 2006;García, 2003;Piontek, 1993; Hayashi, 2008; Zhang, 2009; Wu, 2014; Sato, 2013].

Approximately 30% to 60% of gastric cancers express HER3 [Hayashi, 2008]. HER3 mutations are present in approximately 11% of gastric cancers. In a gastric cancer xenograft model, HER3 antibodies reported to reduce tumor growths. In NCI-N87, an ERBB2 amplified gastric cancer cell line, GSK2849330 treatment restored sensitivity to lapatinib lost due to the addition of NRG1.

Cancers of the Head and Neck

A subset of head and neck cancer cell lines with sensitivity to lapatinib has elevated expression of NRG1 and activation of HER3 [Wilson, 2011]. High NRG1 expression in these cancers is associated with activation of HER3 and may be used as a predictive biomarker for HER3-targeted therapies [Shames, 2013].

A combination of EGFR and HER3 inhibition caused tumor regression in head and neck xenograft models [Zhang, 2014].

NSCLC

NRG1 overexpression was identified as a biomarker for efficacy in patients treated with HER-3 antibody MM-121 [Sequist, 2014]. In a phase 2 trial of patritumab, a HER3-targeted antibody, in combination with erlotinib, an EGFR inhibitor, in erlotinib-naive patients with advanced NSCLC, PFS was significantly improved only in the subgroup of patients with high NRG1 expression [Mendell-Harary, 2014; Von Pawel , 2014]. Furthermore, one PR was confirmed in a patient with NSCLC who expressed high levels of NRG1 in a phase 1 study of HER3 antibody AV-203 that included subjects with advanced or metastatic colorectal cancer, NSCLC, and SCCHN, and other solid tumors [Sarantopoulos, 2014]. Recently, NRG1 gene fusion has been reported in a subset of invasive mucinous lung adenocarcinoma.

Nonclinical data also demonstrated NRG1 induced activation of HER3 signalling adversely affect the activity of agents that target the MEK/MAPK and PI-3K/AKT

signalling pathways. In KRAS mutant NSCLC cell lines, the combined inhibition of MEK and HER3 synergistically induced cell death HER3 is upregulated in response to AKT inhibition in some NSCLC cell lines. In vitro studies of patritumab showed that only cell lines expressing NRG1 responded to treatment, as manifested by decreases in HER3 and AKT phosphorylation [Schneider, 2014].

Section 3.6.3 Rationale for Dose, Dose Escalation

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The proposed dose escalation scheme is based on a half-log step size, **with the exception of the 30 mg/kg/wk dose** and the nominal doses shown in ~~Table 2~~ Table 3 represent the maximum dose which may be selected. The study team, in discussion with the investigator(s), may select ~~lower~~**other** doses **or alternative schedules besides those shown,** ~~than those shown~~ based on emerging safety, tolerability, PK and/or PD data. ~~Additional cohorts may be added to the dose escalation to accommodate intermediate dose levels and slower progression up the dose escalation.~~

Dosing Interval

The predicted half-life for GSK2849330 is ~~8-9~~ **7** days **at 30mg/kg** and is expected to support an every ~~two~~ week ~~(or longer)~~ dosing frequency. However, at lower doses, including the proposed starting dose, the contribution of target mediated clearance may yield a half-life somewhat shorter than projected for higher dose levels. With this consideration, the initial dosing frequency for the first subject will be once-weekly. PK data will be evaluated from the first week of dosing for the first subject, so that adjustments in the dosing interval can be made if appropriate (see the Time and Events Tables Section 7.1 and Section 7.4 for the specific PK assessment schedule for the first subject).

If the half-life appears to be generally in line with expectations, the dosing interval for higher dose cohorts is anticipated to be **every week or** every 2 weeks ~~or every 3 weeks.~~ A general guideline is shown in Table 4. Additional schedules may be explored based on safety, tolerability, PK and PD.

Table 4 Dosing Interval Guidance

Observed half-life	Likely dose interval*
<3 days	Once-weekly
4-8 days	**Every week or** every 2 weeks
> 9 days	Every 3 weeks

*Final selection of dose interval for cohorts will take into consideration the half-life together with safety, tolerability, PK and available PD data.

It is recognized that increasing the dose can allow for extension of the dosing interval with equivalent safety and efficacy, assuming that 1) toxicity is not limited by Cmax and 2) efficacy is related to overall exposure (AUC) or time above a given concentration. Both assumptions appear reasonable for GSK2849330 based on 1) preclinical safety data

and 2) preclinical efficacy data and knowledge of the mechanism of action. Based on human PK predictions from cynomolgus monkey data, a dose of 2.9 mg/kg every 3 weeks IV may provide the same exposure in 3 weeks as 3 doses of 1.2mg/kg every week IV at steady state. Using these principles, it is anticipated that the dosing schedule may be lengthened as appropriate based on accrual of PK and/or PD information.

Additional context for the proposed doses are provided in the following sections.

Human Pharmacokinetic Extrapolation

Human plasma PK was predicted based on extrapolation from PK data of GSK2849330 in cynomolgus monkeys dosed with 1, 10 or 100 mg/kg as a single IV dose (n= 3 female and n= 3 male per group). The estimated terminal half-life from the high dose (100 mg/kg) in a 3-kg cynomolgus monkey was 100-114 h**ours** with central volume of distribution of 140 mL (8% coefficient of variance [CV]) and target mediated clearance equilibrium constant 7.2 µg/mL (57% CV). Single species allometric scaling from 3 kg cynomolgus monkey to a 60 kg human predicts a terminal half-life in humans of approximately 197-224 h**ours** (~8-9 days) with central volume of distribution approximately 2.9 L and equilibrium constant approximately 3.7 µg/mL (57% CV), assuming the same level of target in cynomolgus and human.

Preliminary Human Pharmacokinetic Profile

Preliminary non-compartmental PK parameters are listed in Table 5 below for dose-escalation cohorts in this trial dosed GSK2849330 at 1.4 mg/kg, 3 mg/kg or, 10 mg/kg.

Table 5 Preliminary non-compartmental Pharmacokinetic Profile

Parameter	Unit	n	Treatment (mg/kg)	Estimate (CV%)
AUC(0,336)	hr*µg/mL	1	1.4	3123
		3	3	8880 (25.7)
		3	10	28100 (27.8)
$t_{1/2}$ (24, 168)	hr	1/3	1.4	78.7
$t_{1/2}$ (24, 336)	hr	1/3	3	119
		3	10	134 (32.0)
C_{max}	µg/mL	1	1.4	29.8
		3	3	64.7 (30.2)
		3	10	234 (2.65)
t_{max}	hours	1	1.4	1
		3	3	1 [1-6][a]
		3	10	1[1-6] [a]

AUC = area under the concentration-time curve; Cmax = maximum observed concentration; CV = coefficient of variance; t1/2 = plasma elimination half-life; tmax = time to maximum observed concentration.
Preliminary non-compartmental PK analysis for subjects in dose-escalation cohorts.
a denotes median [range]

Preliminary population PK parameters based on nominal dose and PK sample time are listed in Table 6 below for dose-escalation cohorts at 1.4 mg/kg (n=1), 3 mg/kg (n=2) or, 10 mg/kg (n=2). The data are modelled according to a two compartment PK model with peripheral Target Mediated Drug Disposition. One subject was excluded from the 3 mg/kg cohort because the dose was delayed; and another subject was excluded from the 10 mg/kg cohort because the infusion was terminated early so the total dose of GSK849330 administered was uncertain.

Table 6 Preliminary Population PK Parameters

Parameter	Unit	Estimate	%RSE	%CV
CL	mL/h	11.4	39.1	32.1
V1	mL	2460	6.64	
VM	µg/h	198	40.6	
KM	µg/mL	0.513		
Q	mL/h	79.0	19.1	
V2	mL	2500	13.7	
D1	h	1		
SG1 (proportional)		0.0626	62.9	

The compartmental and non-compartmental model parameters suggest a catabolic half-life of (V1/CL)xln(2) = 150 hours. Considering GSK2849330 as an IgG1-IgG3 fusion with Fc located in the IgG3 region, it is plausible that the elimination half-life is in accordance with the well-known fact that IgG3 elimination half-life is about 7 days (*e.g.*, Stapleton 2011 and references therein).

Predicted Effective Dose

The potential therapeutic dose range for GSK2849330 in humans was derived using available preclinical *in vitro* and *in vivo* PK and efficacy data. In addition, data from mouse *in vivo* CHL-1 xenograft efficacy studies were evaluated to predict the potential minimum clinically efficacious dose. PK/PD modeling of CHL-1 xenograft data in SCID mice suggests that anti-tumor efficacy (based on tumor growth curves) may be achieved with systemic plasma trough concentrations of GSK2849330 maintained at ≥ 20 µg/mL. The predicted human equivalent dose to achieve a similar trough concentration is approximately 1.2 mg/kg/wk. This dose is also in line with that projected, based on *in vitro* potency data, to engage HER3 and inhibit signaling (approximately 0.9 to 5.6 mg/kg). It is anticipated that optimal anti-tumor activity will require full target engagement and that ADCC and CDC enhancements may further increase the anti-tumor activity of GSK2849330. However, it is also recognized that saturation of target throughout the tumor in the clinical setting may require doses higher than those projected based on preclinical extrapolations, due to factors in the tumor microenvironment such as vascular perfusion heterogeneity which may limit mAb intra-tumoral distribution. Recognizing these factors, the top proposed dose for evaluation is 30 mg/kg, a dose which is also viewed as the highest dose feasible based on practical considerations.

A loading dose scenario is predicted to maintain an accumulated steady state trough concentration if the dosing interval is less than or equal to the elimination half-life. Accordingly, a 30 mg/kg weekly IV dose cohort has been added to the dose escalation portion of the study.

Section 3.6.4 Rationale for Endpoints, 4th paragraph

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Tumor, skin, and circulating biomarkers were selected based on the mechanism of action of GSK2849330, preclinical evidence in addition to clinical evidence reported in agents of the same class and in those affecting similar pathways.The objective is to characterize the PD effect of GSK2849330 and to obtain preliminary data on the relationship between HER3 expression levels (i.e., IHC 2+ and 3+), **NRG1 expression,** other potential predictive biomarkers including ~~HER3 ligands,~~ expression of other RTKs, mutations, immune associated markers, and efficacy outcome.

Section 3.9.1.1 Liver Chemistry Follow-up Procedures

REVISED TEXT

Serum acetaminophen adduct high-performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). ~~NOTE: not required in China~~

Section 3.9.2 QTc Stopping Criteria

REVISED TEXT

If a subject meets the QTc[1] interval duration criteria below, study treatment(s) will be withheld.

- QT interval corrected for heart rate (HR) by Fredericia's formula (QTcF) >530 msec

[1]Based on average QTc value of triplicate ECGs to include manual over-read. For example, if an ECG demonstrates a prolonged QT interval, obtain 2 additional ECGs over a brief period (*e.g.,* within approximately 10 minutes of the abnormal ECG, if possible, and approximately 10 minutes apart from each other), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should have study treatment(s) withheld.

If the QTc prolongation resolves to Grade 1 or baseline, the subject may be re-started on the study treatment(s) if the investigator and GSK Medical Monitor agree that the subject will benefit from further treatment.

~~For subjects recruited in France, please refer~~ **Refer** to Appendix 2 for ~~the French specific~~ **country-specific** QTc stopping criteria.

Section 3.10 Guidelines for Events of Special Interest and Dose Modifications, 2nd paragraph

NEW TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

In subjects experiencing suspected infusion-related reactions, a whole blood sample for selected cytokines (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours and submitted to the central laboratory for analysis (see SPM for instructions).

Section 3.10.1 Management of Infusion Reactions

REVISED TEXT

As there is a risk of infusion reactions during administration of IV immunoglobulins, including monoclonal antibodies, subjects will be monitored for signs and symptoms of an infusion-related reaction (including Grade 1 to 2 fever, chills, headache, nausea, malaise) during infusion and for a minimum of 1 hour after the first administration of GSK2849330.

If an infusion-related reaction occurs during administration, the infusion rate may be reduced or halted at the discretion of the investigator and/or GSK medical monitor, depending on the severity of the symptoms and the subject will receive appropriate medical treatment. For subsequent infusions, the investigator may provide premedication with antihistamines, acetaminophen

Treatment may include:

- Fevers/Myalgia: ~~Use acetaminophen.~~**Initiate treatment with acetaminophen (paracetamol).** If subject's fever does not respond to acetaminophen, consider a nonsteroidal anti-inflammatory drug (NSAID) such as indomethacin. Consider ~~pre-medicate~~ **premedication** with acetaminophen ~~(paracetamol)~~ for subsequent doses.

- Chills/rigors: Use warning blankets as initial ~~maneuver~~ **intervention**;, consider IV meperidine (pethidine) if chills persist.

- Nausea/vomiting: **Consider treatment with** 5-HT3 antagonists, prochlorperazine, lorazepam; some agents may cause hypotension and altered mental status, therefore, **these agents should be** use**d** with caution.

3.10.2 Title

REVISED TEXT

Allergic Reaction **Monitoring and** Management

Section 3.10.3 Diarrhea Management

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

If episodes of diarrhea occur, causes for the diarrhea other than the study treatment such as concomitant medications (e.g., stool softeners, laxatives, antacids, etc.), infections by ***Clostridium***. *difficile* or other pathogens, partial bowel obstruction, etc., should be ruled out. **Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.** Supportive measures **depend on the severity of the diarrhea and could** ~~should~~ include the following as clinically indicated:

- Dietary modifications (e.g., small, frequent meals, low fiber, ~~and~~ lactose-avoidance, **and addition of foods rich in potassium**)
- Maintain hydration with clear liquids or IV fluids as needed
- Loperamide and/or oral antibiotics
- **Second-line agents**
- **Hold GSK2849330**

Additional recommended guidelines for the treatment of study treatment induced diarrhea are provided in Benson, et.al. [Benson, 2004] and in Appendix 9

Section 3.10.4 Dose Modifications, 1st paragraph

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

In the event of a toxicity that meets the **guidelines for DLT (Section 3.3.1.)** ~~severity criteria of DLT~~ or is otherwise **considered to be** clinically significant **by the treating physician,** treatment will be stopped and supportive therapy administered as clinically indicated. If clinically significant drug-related toxicity is present, treatment should be delayed until the toxicity resolves (with or without supportive therapy) to baseline or ≤Grade 1. If the toxicity does not resolve to ≤Grade 1 or baseline within 2 weeks, withdrawal from the trial is recommended unless otherwise agreed to by a GSK Medical Monitor and the investigator based on evidence of clinical benefit.

For subjects enrolled in the 30 mg/kg weekly dosing cohort, the dosing frequency may be reduced to every 2 weeks at the discretion of the investigator for a toxicity that does not automatically necessitate a dose reduction.

Section 3.10.4 Dose Modifications, 2nd paragraph

NEW TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For subjects enrolled in the 30 mg/kg weekly dosing cohort, the dosing frequency may be reduced to every 2 weeks at the discretion of the investigator for a toxicity that does not automatically necessitate a dose reduction.

Section 3.10.5 Dose Reductions

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Part 1: A subject who experiences a toxicity **at any time during treatment with GSK2849330 that either meets the guidelines for DLT (Section 3.3.1) or is otherwise considered to be clinically significant by the treating physician, should** ~~meeting the definition of a DLT at any time during treatment with GSK2849330 will~~ have their dose reduced to the previously tested next lower dose level. Any subject who experiences one or more recurrent clinically significant toxicities after the initial dose reduction may have one further dose reduction except where noted otherwise. Subjects who continue to experience clinically significant toxicity despite two dose reductions (i.e., unacceptable toxicity) will be discontinued from the study.

Part 2: Subjects who begin the selected dose and require a dose reduction (due to tolerability/toxicity issues), should be dose reduced to one level below the recommended Part 2 dose. Further dose reductions should be discussed with the GSK Medical Monitor

Section 4: Investigational Products

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The term 'study treatment' is used throughout the protocol to describe the investigational product (IP) received by the subject as per the protocol design **The study was initiated with vials containing 1 mL of IP. Vials containing 5 mL were later introduced, and for the remainder of the study, both 1-mL and 5-mL vials will be available.**

Section 4.1 Description of Investigational Product(s), Table

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Product name :	**GSK2849330 solution for infusion 100 mg/mL**
Formulation description:	Solution containing 100 mg/mL GSK2849330 in vials containing 1 mL for injection **or** **Solution containing 100 mg/mL GSK2849330 in vials containing 5 mL for injection**
Dosage form :	Solution for Infusion. The solution is stored at 2-8°C.
Unit dose strength(s)/Dose Level(s):	IV/100 mg/mL (refer to Section 3.3 and Section 3.4 for dose levels)
Physical Description:	GSK2849330 solution for infusion is clear to opalescent, pale yellow or pale brown in color.
Route/ Administration/ Duration:	Delivered as an IV solution (see Section 3.8).
Dosing instructions:	Dilute GSK2849330 solution into a 0.9% sodium chloride IV bag to the appropriate concentration for the dose. Deliver the entire contents of the IV bag to the subject.
Manufacturer/ Source of Procurement:	GSK

Section 4.2 Preparation/Handling/Storage of GSK2849003 GSK Investigational Product, Preparation

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Preparation

Dilute GSK2849330 solution into a 0.9% sodium chloride IV bag to the appropriate concentration for the dose. Deliver the entire contents of the IV bag to the subject.The administration kits can be polymerizing vinyl chloride (PVC), polyolefin (PO) **plastics** ~~or 0.22µM polyethersulfone (PES). A filtration set will not be used for this study.~~ **A 0.22-µM polyethersulfone (PES) filtration set will be used for this study.**

Section 5.1 Number of Subjects

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The number of dose levels and the level at which the MTD is reached cannot be determined in advance. An adequate number of subjects will be enrolled into the study to establish the recommended dose(s) for further study. It is estimated that approximately ~~10~~**13** subjects will be enrolled in Part 1 dose escalation if there are no DLTs observed; if there are any DLTs observed, more than ~~10~~ **13** subjects can be enrolled in dose escalation. Up to an additional 21 subjects with evaluable pre- and on-treatment paired biopsies can be enrolled for the purpose of the PK/PD cohorts in Part 1. Therefore, up to approximately ~~31~~ **34** subjects may be enrolled into Part 1 (dose-escalation and PK/PD cohorts) of the study; **however additional dose escalation cohorts may be enrolled to allow for further evaluation of additional dose levels/regimens if warranted**.

In Part 2 of the study, there will be at least 4 molecularly-defined tumor histology expansion groups. It is estimated that a minimum of 12 subjects will be enrolled in **each expansion group with a maximum of approximately 30subjects if futility criteria are not met.** ~~Part 2 (expansion cohorts) with a maximum of approximately 90 subjects if all three expansion cohorts are opened and futility criteria were not met.~~ Therefore, ~~up to~~ approximately ~~121~~ **120** subjects may be enrolled in **Part 2 and approximately 154 subjects may be enrolled in** the entire study; however, this number will be considerably fewer if futility conditions are met for any group in the expansion phase (see Section 3.4, Section 13.2.2, and Section 13.6.2). Additional subjects/cohorts may be enrolled to allow for further evaluation of additional dose levels if warranted. **Additional groups of tumor histologies predicted to be sensitive to the study drug based on emerging nonclinical or clinical data may be added to Part 2.**

In Part 1 (dose escalation) of the study, if subjects prematurely discontinue for reasons other than toxicity, additional subjects may be enrolled as replacement subjects and assigned to the same treatment cohort at the discretion of the Sponsor in consultation with the investigator. Subjects may also be replaced in Part 2 of the study for the purpose of testing futility or to facilitate collection of sufficient tumor biopsies for exploratory analyses.

Section 5.2.1, Pre-screening Inclusion Criteria for Part 1

REVISED TEXT

Pre-screening Inclusion Criteria for Part~~s~~ 1 ~~and 2~~

Subjects will be eligible for inclusion in pre-screening for the study (See Section 3.2) only if all of the following criteria apply:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. Performance Status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 3).
4. Sufficient archival tumor specimen is available for HER3 IHC analysis, or subject is willing to undergo a fresh tumor biopsy for HER3 IHC analysis (see Section 7.6.1.1 for details).
5. Histologically or cytologically confirmed diagnosis of one of the following solid tumor malignancies for which no standard therapeutic alternatives exist:
    - Bladder cancer
    - Breast cancer
    - Castrate-resistant prostate cancer
    - Cervical cancer
    - Colorectal cancer (CRC)
    - Gastric cancer
    - Hepatocellular carcinoma (HCC)
    - Melanoma
    - Non-small cell lung cancer (NSCLC)
    - Ovarian cancer
    - Pancreatic cancer
    - Squamous cell cancers of the head and neck region **(SCCHN)(**including parotid and nasopharynx)

Section 5.2.2 Pre-screening for Part 2

NEW TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects with either melanoma, gastric/gastroesophageal cancer, head and neck cancer, or NSCLC who appear to meet all inclusion and exclusion criteria may be pre-screened for the study provided that sufficient tumor specimen is available for analyzing HER3 by IHC or HER3 by IHC and NRG1 by RNA analysis.

Section 5.2.3 Screening Inclusion Criteria for Parts 1 and 2, Criterion 3

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

15. **For subjects enrolled in Part 1:subjects** ~~Subjects~~ must have tumors with documented HER3 expression (2+ or 3+) on the cell surface of the invasive component of tumor (either on archival tissue or fresh tumor biopsy) using an analytically validated IHC assay by central laboratory (see Section 7.6.1.1 for details). **Subjects enrolled in Part 2 must meet inclusion criterion 9 listed below.**

Section 5.2.3 Screening Inclusion Criteria for Parts 1 and 2, Criterion 5

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

5. Adequate baseline organ function defined by:

SYSTEM	LABORATORY VALUES
Hematologic	
ANC	≥1.5 x 10^9/L
Hemoglobin	≥9 g/dL
Platelets	≥75 x 10^9/L
PT/INR and	≤1.3x ULN[c]
Hepatic	
Albumin	≥2.5 g/dL
Total bilirubin	≤1.5 X ULN
AST and ALT	≤2.5 X ULN
Renal	
Serum creatinine OR Estimated glomerular filtration rate or 24-hr urine creatinine clearance[a]	≤ULN OR ≥50 mL/min
Cardiac	
LVEF	≥50% by ECHO or MUGA

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ECHO = echocardiogram; INR = international normalized ratio; LVEF = left ventricular ejection fraction; MUGA = multiple-gated acquisition scan; PT = prothrombin time; PTT = partial thromboplastin time; ULN = upper limit of normal.

a.Estimated glomerular filtration rate will be calculated by the Modification of Diet in Renal Disease (MDRD) equation (Appendix 4). When both a calculated and 24-hr creatinine clearance are available, the 24-hr value will be used.

bECHO is the preferred method. **MUGA should be performed only if evaluation by ECHO is not available.**..

Section 5.2.4 Inclusion Criteria for Part 2 ONLY

NEW TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

As listed above for Part 1, with the exception of criterion 3 which should be replaced with the following criterion 9 and the addition of criteria 10 and 11.

Criterion 9

9. **For Group 1: subjects with previously treated, unresectable stage III or IV melanoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor (either on archival tumor or fresh tumor biopsy) using an analytically validated IHC assay by central laboratory.**

    - **Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).**
        - **Subjects with BRAF V600 mutations who already received or were intolerant of prior BRAF inhibitor therapy may be included.BRAF V600 inhibitor-naïve subjects will be eligible if a BRAF inhibitor is not available to them commercially or via a clinical trial.**
    - **Subjects may be included if they had prior immune therapy, were intolerant of prior immune therapy, or if such therapy is not available to them commercially or via a clinical trial.**

    For Group 2: Subjects with previously treated, unresectable stage III or IV gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor (either on archival tumor or fresh tumor biopsy) using an analytically validated IHC assay by central laboratory.

    - **Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).**
    - **Subjects with HER2 positive disease may be included if they had prior anti-HER2 therapy or were intolerant of prior anti-HER2 therapy or if such therapy is not available to them commercially or via a clinical trial.**

    For Group 3: Subjects with previously treated, unresectable stage III or IV cancers of the head and neck with documented HER3 expression (≥1+) and NRG1 expression on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy) using analytically validated assays by central laboratory.

- **Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).**
- **Subjects with locoregional recurrences amenable to definite surgery or additional radiation are excluded.**

For Group 4: Subjects with previously treated, unresectable stage III or IV NSCLC with documented HER3 expression (≥1+) and NRG1 expression on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy) using analytically validated assays by central laboratory.

- **Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1.).**
- **Subjects with anaplastic lymphoma kinase (ALK) translocation who already received or were intolerant of prior anti-ALK therapy may be included.Anti-ALK therapy-naïve subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.**
- **Subjects with EGFR mutations (e.g., exon 19 deletion and exon 21 L858R) who have documented progression (based on RECIST 1.1 criteria) or who were intolerant of prior EGFR inhibitors may be included.EGFR inhibitor-naive subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.**

Additional tumor histology groups predicted to be sensitive to the study drug based on biomarkers (e.g., HER3 mutations, NRG translocations) supported by preclinical or clinical data may be added based on emerging data.

Criterion 10

Subjects must have at least one measurable lesion per RECIST v1.1.

NOTE: If the only site of measurable disease has been previously irradiated, documented progression of disease and a 4-week interval since completion of radiotherapy is required.
NOTE: In subjects with ≥1 measurable lesion, a measurable lesion may be biopsied at Screening and Day 15; however that lesion must not be selected as a target lesion for disease assessment.

Criterion 11

Subjects must have disease amendable to biopsy and agree to undergo pre- and on-treatment tumor biopsies (until the participating centers receive

written notification from the Sponsor that paired tumor biopsies are no longer required).

Section 5.2.5 Screening Exclusion Criteria Parts 1 and 2, Criterion 1

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

1. Subjects with leptomeningeal or brain metastases or spinal cord compression.

    - **Subjects with untreated brain or meningeal metastases are not eligible (computed tomography [CT] scans are not required to rule this out unless there is a clinical suspicion of central nervous system [CNS] disease.**
    - **Subjects with treated and radiologic or clinical evidence of stable brain metastases (confirmed by 2 scans at least 4 weeks apart), with no evidence of cavitation or hemorrhage in the brain lesion are eligible providing that they are asymptomatic and do not require corticosteroids. Subjects are not permitted to receive enzyme inducing anti-epileptic drugs.**

Section 5.2.5 Screening Exclusion Criteria Parts 1 and 2, Criterion 3

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

3. Use of an investigational anti-cancer drug within 28 days **or 5 half-lives, whichever is longer**, preceding the first dose of GSK2849330 OR chemotherapy within the last 3 weeks (6 weeks for prior nitrosourea or mitomycin C) OR any major surgery, radiotherapy, immunotherapy or any other anti-cancer therapy within the last 4 weeks **except as noted above**.

Section 5.2.5 Screening Exclusion Criteria Parts 1 and 2, Criterion 7

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

7. History or evidence of significant cardiovascular risk including any of the following:

    - LVEF <50%
    - A QT interval corrected for HR ~~using the Fredericia's formula~~ (QTc) ≥480 msec (≥500 msec for subjects with bundle branch block)
    - History or evidence of current clinically significant uncontrolled arrhythmias.

    Exception: Subjects with controlled atrial fibrillation for >30 days prior to enrollment are eligible.

    - History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within 6 months prior to enrollment.

- History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA).

Section 6.2 Subject Completion Criteria

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

~~A subject will be considered to have completed the study if they complete screening assessments and one study treatment.~~ **In Part 1, a subject will be considered to have completed the study if they complete screening assessments and at least one study treatment followed by at least 28 days of observation. In Part 2, a subject will be considered to have completed the study if they have completed at least one on-treatment disease assessment.**

Section 6.3 Permanent Discontinuation from Study Treatment

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects will receive study treatment until disease progression, death or unacceptable toxicity, including meeting stopping criteria for liver chemistry defined in Section 3.9.1 .In addition, study treatment ~~may~~**will** be permanently discontinued for any of the following reasons

- major deviations(s) from the protocol
- request of the subject or proxy (withdrawal of consent by subject or proxy)
- investigator's discretion
- a dose delay for toxicity of > 2 weeks unless the investigator or GSK Medical Monitor agree that further treatment may benefit the subject
- intercurrent illness that prevents further administration of study treatment
- subject is lost to follow-up, or the study is closed or terminated.

The primary reason study treatment was permanently discontinued must be documented in the subject's medical records and eCRF.

If the subject voluntarily discontinues from treatment due to toxicity, 'AE' will be recorded as the primary reason for permanent discontinuation on the eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated.

All subjects who discontinue from study treatment will have safety assessments at the time of discontinuation and during post-study treatment follow-up as specified in Time and Events Tables (see Section 7.1).

Section 6.4 Study Completion

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The study will be considered completed, that is, having met the study objectives, after 70% of the subjects have died or 2 years after the last subject is enrolled. Upon completion of the study, if subjects are still continuing to receive benefit from GSK2849330, plans will be developed to provide continued access for those subjects if warranted.

Per the EU Clinical Trial Directive, the end of the study is defined as the last subject's last visit (LSLV).

Section 7 Study Assessments and Procedures

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments being performed. Procedures conducted as part of the subject's routine clinical management (*e.g.*, blood count, ECG, ECHO/MUGA) obtained prior to their signing the informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol and have been performed within the protocol-specified timeframe. However physical exam, medical history, ECOG performance status, and vital signs must be conducted after the informed consent is signed regardless of when these procedures may have been performed as part of routine clinical management.

The timing of each assessment is listed in the Time and Events Tables (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for safety, PK, PD/biomarker, immunogenicity, imaging or other assessments. Changes in timing, addition, or removal of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 200 mL of blood will be collected over a 30-day period, including any extra assessments that may be required.

Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. The timing of the assessments should allow the blood draw to occur at the exact nominal time. Detailed procedures for obtaining each assessment are provided in the SPM.

After a subject has provided written informed consent for pre-screening, the investigator or other study personnel will determine if the subject is eligible for pre-screening in the study. This will be done by reviewing the pre-screening inclusion criteria (Section 5.2.1) and completing all of the pre-screening assessments outlined

in the Time and Events Table (Section 7.1). Pre-screening assessments may be carried out over more than one day.

If during pre-screening the subject is determined to have **the required** ~~a~~ tumor expressing HER3 **or HER3 and NRG1 levels of expression** ~~(see Inclusion criteria 3),~~ then after a subject has provided written informed consent for the study and within 14 days of the first dose of study treatment, the investigator or other study personnel will determine if the subject is eligible for enrollment in the study. .This will be done by reviewing the inclusion and exclusion criteria and completing all of the screening assessments outlined in the Time and Events Tables (Section 7.1). Screening assessments may be carried out over more than one day provided that all required assessments are completed within14 days prior to the first dose of study treatment.

Section 7.1 Time and Events Tables

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~**)**

Table 7 Time and Events for Part 1 (Dose Escalation Cohorts, every 2 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)			Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 8	Day 15				
		-14 day window[3]		± 1 day window for each visit		± 1 day window	± 3 day window for each visit	± 7 day window	+ 7 day window
Informed consent	X	X							
Archival tissue	X								
Tumor biopsy	X[4]	X[5]			X[6] pre-dose			X[7]	
Skin biopsy			X pre-dose		X pre-dose				
Baseline demographics	X	X							
Medical history	X	X	X					X	
Concurrent medication	Continuous							X	
Pregnancy test[8]		X[3]				X pre-dose	Every 4 weeks ~~from day 29~~	X	X
Physical examination		X	X[9]		X	X	Every 4 weeks ~~from day 29~~	X	
Height (at screening only) and weight		X	X			X	Weight: Every 4 weeks ~~from first dose~~	X	
ECOG	X	X	X[9]			X	Every 4 weeks ~~from first dose~~	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X	X	X	Every 2 weeks ~~from day 29~~[10]	X	
12-lead ECG		X	X[10]		X	X	Every 4 weeks ~~from day 29~~	X	
Hematology/Clinical Chemistry		X	X[9]	X	X	X	Every 2 weeks ~~from day 29~~	X	

	Pre-screening	Screening	First Treatment Period (28 days)			Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 8	Day 15				
		-14 day window[3]		± 1 day window for each visit		± 1 day window	± 3 day window for each visit	± 7 day window	+ 7 day window
Coagulation parameters PT, INR, PTT		**X**	**As Clinically Indicated**						
Urinalysis		X				X	Every 4 weeks ~~from day 29~~	X	
ECHO[11]		X				X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	Every 12 weeks ~~from the first dose~~	X[7]	X
Circulating cell free DNA (cfDNA)			X pre-dose					X[7]	
Testosterone and LH[13]			X pre-dose			X	Every 8 weeks ~~from day 29~~		
Whole blood/serum /cellular markers[14]			X	X	X	X		X[7]	
GSK2849330 IV infusion[15]			X		X	X	Every 2 weeks[15] ~~from the first dose~~		
AE assessment	Continuous								
Serum sample for Immunogenicity			X pre-dose	X		X	Every 12 weeks[16] ~~from the first dose~~		X[16]
PGx sample			X pre-dose[17]						
Tumor markers [18]			X				Every 8 weeks ~~from the first dose~~		
Disease assessment[19]		X[3]					Every 8 weeks ~~from the first dose~~	**X**[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.

5. Fresh pre- and on-treatment tumor biopsy is optional, but strongly encouraged for dose escalation cohorts; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated on Day 1. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is optional on Day 15 for dose escalation cohort subjects and required for the PK/PD cohorts. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. **Tumor biopsy is optional and only collected for subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to the start of any subsequent anticancer therapy.**
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose,and at 1, 2, 4, and 6 hours after the start of infusion. ~~For subjects in Cohort 1 on a weekly dosing schedule vital signs should be conducted weekly at each dosing visit in clinic.~~
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1hour (± 15-minute window), and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. Additional PK samples will be collected at Day 8, Day 15, and Day 29. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year samples will be collected every 24 weeks. An additional PK sample will also be taken at the Post-study visit. ~~On days of dosing sample will be drawn pre-dose.~~**Unless stated otherwise, on days of dosing sample will be drawn pre-dose.** For the first subject in Cohort 1 additional PK samples will be taken at 24 hours (Day 2 [± 8-hour window]) and at 72 hours (Day 4 [± 24-hour window]) after the end of infusion of the first dose of GSK2849330.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hour (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For the subject(s) in Cohort**s** 1 **and 5,** and any subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2-week or every 3 week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subject (s) in Cohort 1 will receive the dose weekly in clinic. Cohorts 2-4 will receive the dose every 2 weeks. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. After the first treatment period, immunogenicity samples will be collected every 12 weeks from the first dose within one year of treatment. If treatment continues after 1 year, samples will be collected every 24 weeks. An immunogenicity sample must also be collected at the Post-study visit.

17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. **A blood sample for select serum safety markers (including, but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.**
21. **Disease assessment must be performed either at the Follow up visit or at the Post-Study visit prior to the start of any subsequent anti-cancer therapy.**

NEW TEXT

Table 8 Time and Events for Part 1 (Dose Escalation Cohorts, every week dosing schedule)

	Pre-screen	Screen	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 2	Day 4	Day 8	Day 15	Day 22				
		-14 day window[3]				± 1 day window for each visit				± 2 day window for each visit	+ 7 day window	
Informed consent	X	X										
Archival tissue	X											
Tumor biopsy	X[4]	X[5]					X[6] pre-dose				X[7]	
Skin biopsy			X pre-dose				X pre-dose					
Baseline demographics	X	X										
Medical history	X	X	X									

	Pre-screen	Screen	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 2	Day 4	Day 8	Day 15	Day 22				
		-14 day window[3]				± 1 day window for each visit				± 2 day window for each visit	+ 7 day window	
Concurrent medication	Continuous											
Pregnancy test[8]		X[3]							X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X						X	Weight: Every 4 weeks	X	
ECOG		X	X[9]						X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	X	X	Every week[22]	X	
12-lead ECG		X	X[10]				X		X	Every 4 weeks	X	
Hematology/ Clinical Chemistry		X	X[9]			X	X	X	X	Every week[22]	X	
Coagulation parameters: PT, INR, PTT		X	As clinically indicated									
Urinalysis		X							X	Every 4 weeks	X	
ECHO[11]		X							X	Every 8 weeks	X	

	Pre-screen	Screen	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 2	Day 4	Day 8	Day 15	Day 22				
		-14 day window[3]	± 1 day window for each visit							± 2 day window for each visit	+ 7 day window	
PK (Blood)[12]			X	X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction									
Circulating cell free DNA (cfDNA)			X pre-dose								X[7]	
Testosterone and LH[13]			X pre-dose						X	Every 8		
Whole blood/serum /cellular markers[14]			X			X	X		X		X[7]	
GSK2849330 IV infusion[15]			X			X	X	X	X	Every week[15]		
AE assessment			Continuous									
Serum sample for Immunogenicity			X pre-dose								X[16]	X[16]
PGx sample			X pre-dose[17]									
Tumor markers [18]			X							Every 8 weeks		
Disease assessment[19]		X[3]								Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.

5. Fresh pre- and on-treatment tumor biopsy is optional, but strongly encouraged for dose escalation cohorts; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is optional on Day 15 for dose escalation cohort subjects and required for the PK/PD cohorts. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected for subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose, and at 1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose, and at 1 hour (± 15-minute window), 6 hour (± 1-hour window) and 24 hours after the end of infusion. Pre-dose samples will also be collected on Day 4, Day 8 and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter. If treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up and Post-study visits.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For the subjects in Cohorts 1 and 5, and any subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2 week or every 3 week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.

19. **Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.**
20. **A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.**
21. **Disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy**
22. **Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen**

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Table 9 Time and Events for Part 1 PK/PD Cohorts (every 2 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15				
			Day 1	Day 2	Day 4	Day 8					
		- 14 day window[3]				± 1 day window for each visit			± 3 day window for each visit		+ 7 day window
Informed consent	X	X									
Archival tissue	X										
Tumor biopsy	X[4]	X[5]					X[6] pre-dose			X[7]	
Skin biopsy			X pre-dose				X pre-dose				
Baseline demographics	X	X									
Medical history	X	X	X								
Concurrent Medication	Continuous									X	
Pregnancy test[8]		X[3]						X pre-dose	Every 4 weeks ~~from day 29~~	X	X
Physical examination		X	X[9]				X	X	Every 4 weeks ~~from day 29~~	X	

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15				
			Day 1	Day 2	Day 4	Day 8					
		- 14 day window[3]				**± 1 day window for each visit**			**± 3 day window for each visit**		**+ 7 day window**
Height (at screening only) and weight		X	X					X	Weight: Every 4 weeks ~~from first dose~~	X	
ECOG	X	X	X[9]					X	Every 4 weeks ~~from day 29~~	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X	X	X	X	X	Every 2 weeks ~~from day 29~~[10]	X	
12-lead ECG		X	X[10]				X	X	Every 4 weeks ~~from day 29~~	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	Every 2 weeks ~~from day 29~~	X	
Coagulation parameters PT, INR, PTT		X	As Clinically Indicated								
Urinalysis		X						X	Every 4 weeks ~~from day 29~~	X	
ECHO[11]		X						X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	Every 12 weeks ~~from the first dose~~	X[7]	X
cfDNA			X pre-dose							X[7]	
Testosterone and LH[13]			X pre-dose					X	Every 8 ~~weeks from day 29~~		
Whole blood/serum /cellular markers[14]			X	X		X	X	X		X[7]	
GSK2849330 IV infusion[15]			X				X	X	Every 2 weeks[15] ~~from the first dose~~		
AE assessment	Continuous										
Serum sample for Immunogenicity			X pre-dose			X		X	Every 12 weeks[16] ~~from the first dose~~	X[16]	X[16]

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15				
			Day 1	Day 2	Day 4	Day 8					
		- 14 day window[3]				**± 1 day window for each visit**			**± 3 day window for each visit**		**+ 7 day window**
PGx Sample[17]			X pre-dose								
Tumor markers [18]			X						Every 8 weeks ~~from the first dose~~		
Disease assessment[19]		X[3]							Every 8 weeks ~~from the first dose~~		

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 15 dose.
7. Collected at progression. **Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.**
8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose, and at 1, 2, 4, and 6 hours after the start of infusion.~~For subjects in Cohort 1 on a weekly dosing schedule vital signs should be conducted weekly at each dosing visit in clinic.~~
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) ~~and~~ 6 hours (± 1-hour window) **and 24 hour** after the end of infusion. ~~If a subject's duration of infusion is 3 hours or longer the 6 hr time point is optional. Additional PK samples will be collected at 24 hr (Day 2 [± 8 hr window]), 72 hr (Day 4 [± 24 hr window]) after the end of infusion, and on Day 8, Day 15, and Day 29 after the first dose of GSK2849330. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after~~

~~1 year samples will be collected every 24 weeks. An additional PK sample will also be taken at the Post-study visit. On days of dosing sample will be drawn pre-dose~~**. Pre-dose samples will also be collected on Day 4, Day 8 and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.**

13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window), and 24 hours (Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer, the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will be collected at progression.
15. ~~For the subject(s) in cohort 1 and any subjects receiving a weekly dosing schedule the study treatment dosing window is ± 2 days. Subject(s) in Cohort 1 will receive the dose weekly in clinic.~~ The study treatment dosing window is ± 3 days for subjects on an every 2-week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. ~~Cohorts 2-4 will receive the dose every 2 weeks.~~ Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. ~~After the first treatment period, immunogenicity samples will be collected every 12 weeks from the first dose within 1 year of treatment. If treatment continues 1 year, samples will be collected every 24 weeks.~~ An immunogenicity sample ~~must also be collected at the Post-study visit~~ **will be collected at the Follow up and Post-study visits.**
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subjects' primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. **A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.**
21. **Disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.**

NEW TEXT

Table 10 Time and Events for Part 1 PK/PD Cohorts (every week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22				
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]	± 1 day window for each visit							± 2 day window for each visit	+ 7 day window	
Informed consent	X	X										
Archival tissue	X											
Tumor biopsy	X[4]	X[5]					X[6] pre-dose				X[7]	
Skin biopsy			X pre-dose				X pre-dose					
Baseline demographics	X	X										
Medical history	X	X	X									
Concurrent Medication	Continuous										X	
Pregnancy test[8]		X[3]							X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X						X	Weight: Every 4 weeks	X	
ECOG		X	X[9]						X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X	X	X	X		X	Every week[22]	X	

	Pre-screening	Screening	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22				
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]				± 1 day window for each visit				± 2 day window for each visit	+ 7 day window	
12-lead ECG		X	X[10]				X		X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	X	Every week[22]	X	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated									
Urinalysis		X							X	Every 4 weeks	X	
ECHO[11]		X							X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction									
cfDNA			X pre-dose								X[7]	
Testosterone and LH[13]			X pre-dose						X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X		X	X		X		X[7]	
GSK2849330 IV infusion[15]			X			X[15]	X	X	X[15]	Every week[15]		
AE assessment	Continuous											
Serum sample for Immunogenicity			X pre-dose								X[16]	X[16]
PGx Sample[17]			X pre-dose									

	Pre-screening	Screening	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22				
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]				**± 1 day window for each visit**				**± 2 day window for each visit**	**+ 7 day window**	
Tumor markers [18]			X							Every 8 weeks		
Disease assessment[19]		X[3]								Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 15 dose.
7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose, and at 1, 2, 4, and 6 hours after the start of infusion. For subjects on a weekly dosing schedule, vital signs should be conducted weekly at each dosing visit in clinic.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected Day 1: pre-dose, and at 1 hour (± 15-minute window), 6 hours (± 1-hr window) and 24 hours after the end of infusion. Pre-dose samples will also be collected on Day 8 and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.
13. To be conducted in male subjects only.

14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window), and 24 hours (Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer, the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will be collected at progression.
15. For the subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days The study treatment dosing window is ± 3 days for subjects on an every 2 week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. Disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

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Table <u>11</u> Time and Events for Part 1 PK/PD Cohorts (every 3 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (21 days)					Continuation Phase	Follow-up[1]	Post-study[2]
			First Week							
			Day 1	Day 2	Day 4	Day 8	Day 22			
		- 14 day window[3]				± 1 day window for each visit		± 3 day window for each visit		+7 day window
Informed consent	X	X								
Archival tissue	X									
Tumor biopsy	X[4]	X[5]					X[6]pre-dose		X[7]	
Skin biopsy			X pre-dose				X pre-dose			
Baseline demographics	X	X								
Medical history	X	X	X						X	
Concurrent medication	Continuous								X	
Pregnancy test[8]		X[3]					X pre-dose	Every 3 weeks ~~from day 22~~	X	X
Physical examination		X	X[9]				X	Every 3 weeks ~~from day 22~~	X	
Height (at screening only) and weight		X	X				X	Weight: Every 3 weeks ~~from day 22~~	X	
ECOG	X	X	X[9]				X	Every 3 weeks ~~from from day 22~~	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X	X	X	X	Every 3 weeks ~~from day 22~~	X	
12-lead ECG		X	X[10]				X	Every 3 weeks from day 22	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	Every 3 weeks ~~from day 22~~	X	
Urinalysis		X					X	Every 3 weeks ~~from day 22~~	X	
ECHO[11]		X					X	Every 9 weeks ~~from day 22~~	X	

	Pre-screening	**Screening**	**First Treatment Period (21 days)**					**Continuation Phase**	**Follow-up[1]**	**Post-study[2]**
			First Week							
			Day 1	**Day 2**	**Day 4**	**Day 8**	**Day 22**			
		- 14 day window[3]				**± 1 day window for each visit**		**± 3 day window for each visit**		**+7 day window**
PK (Blood)[12]			X	X	X	X	X	X Day 43 and every 12 weeks ~~from the first dose~~	X[7]	X
cfDNA			X pre-dose						X[7]	
Testosterone and LH[13]			X pre-dose				X	Every 9 weeks ~~from day 22~~		
Whole blood/serum /cellular markers[14]			X	X		X	X	Day 43	X[7]	
GSK2849330 IV infusion[15]			X				X	Every 3 weeks[15] ~~from the first dose~~		
AE assessment	Continuous									
Serum sample for Immunogenicity			X pre-dose			X	X	Every 12 weeks[16] ~~from the first dose~~		X[16]
PGx Sample[17]			X pre-dose							
Tumor markers [18]			X					Every 9 weeks ~~from the first dose~~		
Disease assessment[19]		X[3]						Every 9 weeks ~~from the first dose~~		

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and disease assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 22 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 22 dose.
7. Collected at progression. **Tumor biopsy is optional and only required from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.**

8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 22 and every 3 weeks from Day 22 in the continuation phase of the study.
9. If completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose, and at 1, 2, 4, and 6 hours after the start of infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 9 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. Additional PK samples will be collected at 24 hours (Day 2 [± 8-hour window]) and 72 hours (Day 4 [± 24-hour window]) after the end of infusion, and at Day 8, Day 22, and Day 43 [± 1-day window] after the first dose of GSK2849330. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year samples will be collected every 24 weeks. An additional PK sample will be collected at the Post-study visit. On days of dosing sample will be drawn pre-dose.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular marker. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window), and 24 hours (Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 22 and Day 43 for all cohorts. An additional blood sample should be collected at progression.
15. The study treatment dosing window is ± 3 days for an every 3 week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received.
16. ~~After the first treatment period, immunogenicity samples will be collected every 12 weeks from the first dose within 1 year of treatment. If treatment continues after 1 year, samples will be collected every 24 weeks.~~ An immunogenicity sample ~~must also be collected at the Post-study visit.~~**will be collected at the Follow-up and Post-study visits.**
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subjects' primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. **A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.**
21. **Disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.**

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Table 12 Time and Events for Part 2 ~~Expansion Cohorts~~ Molecularly-Defined Tumor Histology Groups

	Pre-Screen	Screen	First Treatment Period (28 days)				Day 29	Continuation Phase	Follow up[1]	Post study[2]
			Day 1	Day 8	Day 15	Day 22				
		-14 day window[3]		± 1 day window for each visit				± 2day window for each visit	+ 7 day window	
Informed consent	X	X								
Archival tissue	X									
Tumor biopsy	X[4]	X[5]			X[6] pre-dose				X[7]	
Baseline demographics	X	X								
Medical history	X	X	X							
Concurrent medication	Continuous									
Pregnancy test[8]		X[3]					X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]		X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X				X	Weight: Every 4 weeks	X	
ECOG		X	X[9]				X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X[22]	X	X[22]	X	Every week[10,22]	X	
12-lead ECG		X	X[10]		X		X	Every 4 weeks	X[22]	
Hematology/Clinical Chemistry		X	X[9]	X[22]	X	X[22]	X	Every week[22]	X[22]	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated							
Urinalysis		X					X	Every 4 weeks	X	

	Pre-Screen	Screen	First Treatment Period (28 days)				Day 29	Continuation Phase	Follow up[1]	Post study[2]
			Day 1	Day 8	Day 15	Day 22				
		-14 day window[3]		± 1 day window for each visit				± 2day window for each visit	+ 7 day window	
ECHO[11]		X					X	Every 8 weeks	X	
PK (Blood)[12]			X		X		X	X[12]	X	X
Safety cytokines[20]			In the event of an infusion reaction							
Circulating cell free DNA (cfDNA)			X pre-dose						X[7]	
Testosterone and LH[13]			X pre-dose				X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X[22]	X		X		X[7]	
GSK2849330 IV infusion[15]			X	X[22]	X	X[22]	X	Everyweek[15,22]		
AE assessment			Continuous							
Serum sample for Immunogenicity			X pre-dose						X[16]	X[16]
PGx sample			X pre-dose[17]							
Tumor markers [18]			X					Every 8 weeks		
Disease assessment[19]		X[3]						Every 8 weeks	X[21]	

1. If completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
2. Collect at pre-dose**, and at 1, 2, 4, and 6 hours after the start of the first infusion**.
3. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 ~~or 9~~weeks if clinically indicated.
4. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), after the end of infusion**, and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and every 12 weeks thereafter**. ~~Additional PK samples will be collected pre-dose Day 15 and Day 29 for an every 2 week dosing schedule, and pre-dose Day 22 and Day 43 for an every 3 week dosing schedule, these additional samples all have a ± 1 day window.~~ Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment

continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up or Post-study visits. Unless stated otherwise, on days of dosing sample will be drawn pre-dose.

5. To be conducted in male subjects only.
6. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected **on Day 1**: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. **A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts.** ~~On day 15 for those subjects on a 2 week dosing schedule and on Day 22 pre-dose for those subject s on a 3 week dosing schedule, a blood sample is required to be collected.~~ An additional sample will also be collected at progression.
7. **For the subjects receiving a weekly dosing schedule, the** ~~The~~ study treatment dosing window is ± **2**~~3~~ days. **The study treatment dosing window for all other dosing schedules (*e.g.*, an every 2-week or every 3-week dosing schedule) is ± 3 days.** If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received.
8. ~~After the first treatment period, immunogenicity samples will be collected every 12 weeks from the first dose within 1 year of treatment. If treatment continues after 1 year, samples will be collected every 24 weeks.~~ An immunogenicity sample must be collected at the **Follow-up and** Post-study visits.
9. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
10. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
11. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
12. **A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.**
13. **Disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.**
14. **Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.**

Section 7.3.6 Laboratory Assessments, Table of Clinical Laboratory Tests

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Table 13 List of Clinical Laboratory Tests

Hematology			
Platelet Count		*<u>RBC Indices</u>*:	*<u>Automated WBC Differential</u>:*
Red blood cell (RBC) Count		Mean corpuscular volume (MCV)	Neutrophils
White blood cell (WBC) Count (absolute)		Mean corpuscular hemoglobin (MCH)	Lymphocytes
Reticulocyte Count		Mean corpuscular hemoglobin concentration (MCHC)	Monocytes
Hemoglobin			Eosinophils
Hematocrit			Basophils
Clinical Chemistry			
Blood urea nitrogen (BUN) or urea	Potassium	AST	Total and direct bilirubin
Creatinine	Chloride	ALT	Uric Acid
Glucose, fasting	Total carbon dioxide (CO_2)	Gamma glutamyl transferase (GGT)	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Magnesium	Phosphate		
Routine Urinalysis			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (if blood or protein is abnormal)			
Other tests			
PT, INR, PTT			
Testosterone (male subjects only)			
Luteinizing Hormone (LH) (male subjects only)			
Follicle stimulating hormone (FSH) and estradiol (as needed in women of non-child bearing potential only)			

Section 7.4 Pharmacokinetics

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For ~~all subjects in the dose escalation cohorts in Part 1~~,**<u>subjects enrolled in Part 1, dose escalation Cohorts 1-4,</u>** blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour and 6 hours after the end of infusion and at Day 8, Day 15, and Day 29 after the first dose of GSK2849330. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. On days of dosing, the sample will be drawn pre-dose. Additionally the first subject in Cohort 1 will have PK samples taken at 24 hours (Day 2) and 72 hours (Day 4) after the end of infusion.

For subjects enrolled in the additional dose escalation cohorts enrolled under Amendment 1 of this protocol, more frequent PK samples will be collected on Day 1: pre-dose, and at 1 hour, 6 hours and 24 hours after the end of infusion;. Pre-dose samples will also be collected on Day 4, Day 8, and weekly through Day 57 with additional one hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85, and every 12 weeks thereafter.

For all subjects in the Part 1 PK/PD cohorts, blood samples for analysis of GSK2849330 concentrations will be collected on **scheduled dosing** Day 1: pre-dose and at 1 hour, **6 hours, and 24 hours after the end of the infusion. Pre-dose samples will also be collected on Day 4, Day 8, and weekly through Day 57 with additional one hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.**~~and 6 hr after the end of infusion and at 24 hr (Day 2), 72 hr (Day 4), and 168 hr (Day 8) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hr time point is optional. Additional PK samples will be drawn pre-dose on Days 22 and 43 (after the first dose) for subjects on an every 3 week dosing schedule or pre-dose on Days 15 and 29 (after the first dose) for subjects on an every 2 week dosing schedule. On days of dosing, the sample will be drawn pre-dose.~~

For the expansion ~~cohorts~~**groups** in Part 2, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour after the end of infusion ~~with an additional PK samples pre-dose on Days 22 and 43 (after the first dose) for subjects on an every 3 week dosing schedule or pre-dose on Days 15 and 29 (after the first dose) for subjects on an every 2 week dosing schedule.~~**and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85 and every 12 weeks thereafter**.

For all subjects (Part 1 and Part 2), **if treatment continues beyond 1 year, samples will be collected every 24 weeks**. ~~PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year samples will be collected every 24 weeks~~. An additional PK sample will also be taken **at the Follow-up visit (28 days after the last dose of study treatment) and/or at the Post-study visit [**45 days or 5 half-lives (whichever is longer)] after the last dose of study treatment. ~~On days of dosing sample will be drawn pre-dose.~~ **Unless stated otherwise, on days of dosing PK samples will be drawn pre-dose.**

See the Time and Events Tables Section 7.1 and the SPM for additional details on the PK sample timing.

Section 7.4.1 Blood Sample Collection for Pharmacokinetics

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Blood samples ~~of approximately 1-2mL~~ for PK analysis of GSK2849330 will be collected at the time points indicated in the Time and Events Tables (Section 7.1). Each PK sample should be collected as close as possible to the planned time relative to the

dose (i.e., time zero) administered to the subject on PK days. The actual date and time of each blood sample collection will be recorded.

Section 7.6.1.1, Title

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Tumor Tissue for Pre-screening Assessments and Exploratory Research

Section 7.6.1.1: Tumor Tissue for Pre-screening Assessments and Exploratory Research

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Tumor Tissue for Pre-screening Assessments and Exploratory Research

~~A formalin-fixed, paraffin-embedded~~ **Tumor** tissue ~~block~~ taken ~~at~~**from** a metastatic site (preferably) or obtained at the time of original primary cancer diagnosis (biopsy or from definitive surgery) is required to be submitted ~~to the central laboratory (Ventana Medical Systems)~~ **for analysis to one or more of the central laboratories including Ventana Medical Systems** ~~for determining HER3 expression~~ **to determine HER3 and NRG1 expression.** ~~and for subsequent translational research (regardless of any local results). Alternatively, sites may send 15-20 freshly sectioned, unstained slides containing 5-micron thick sections. Refer to the SPM for details on tumor tissue sample preparation and shipping.~~ . **If archival tumor tissue is not available, a fresh biopsy is required for HER3 and NRG1 testing.** If archival tumor tissue is not available, a fresh biopsy is required for HER3 **and NRG1** testing.

Section 7.6.1.2 Tumor Biopsies

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Every effort should be made to collect pre- and on-treatment tumor biopsies. Image guidance has been shown to significantly increase the probability of success in obtaining tumor biopsies and is required for all percutaneous pre- and on-treatment biopsies in this study (with the exception of melanoma skin lesions or cutaneous metastases of other solid tumors).

Tumor biopsies are optional for subjects in the dose escalation cohorts, but strongly encouraged All subjects enrolled in PK/PD cohorts in Part 1 and in each of the expansion groups in Part 2 must agree to pre and on-treatment tumor biopsies for assessment of PD effect. GSK will closely monitor and evaluate the collection of evaluable biopsies and will notify the participating centers of any change to the collection requirements for any or all groups.

Tumor biopsies for PD analyses will be collected at the time points listed in the Time and Events Tables Section 7.1.

~~All subjects enrolled in PK/PD cohorts in Part 1, must agree to pre and on-treatment tumor biopsies for assessment of PD effect. Tumor biopsies are optional for subjects in~~

~~the dose escalation cohorts, but strongly encouraged. For subjects in Part 2 expansion cohorts see Section 3.4 regarding tumor biopsy requirements. Tumor biopsies for PD analyses will be collected at the time points listed in the Time and Events Tables Section 7.1.~~

Section 7.6.2 Skin Biopsies

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For subjects in Part 1 of the study, every effort should be made to collect pre- and on-treatment skin biopsies for analysis of RNA or protein levels that may indicate a PD response to GSK 2849330. Protein levels that may be analyzed include, but are not limited to, markers of the HER3 pathway such as HER3 and phospho-HER3.

All subjects enrolled in dose escalation and PK/PD cohorts in Part 1 must agree to pre and on-treatment skin biopsies for assessment of PD effect. ~~For subjects in Part 2 expansion cohorts, the consent to pre and on-treatment skin biopsies is optional.~~

Refer to Time and Events Tables in Section 7.1 for details on time points.

Details on skin biopsy collection, processing, storage and shipping procedures are provided in the SPM.

Section 7.8 Evaluation of Anti-Cancer Activity, 1st paragraph

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Disease assessment may include imaging (e.g., CT scan, MRI, bone scan, plain radiography) and physical examination (as indicated for palpable/superficial lesions). Disease assessment will be completed within 4 weeks prior to the first dose of GSK2849330, then every 8 or 9 weeks thereafter, and at the final study visit. See the Time and Events Tables (Section 7.1) for the schedule of assessments of anti-cancer activity. Assessments must be performed on a calendar schedule and should not be affected by dose interruptions/delays. For post-baseline assessments, a window of ±7 days is permitted to allow for flexible scheduling If the last radiographic assessment was more than 8 weeks prior to the subject's withdrawal from study and progressive disease (PD) has not been documented, **and the subject has not started subsequent anti-cancer therapy,** a disease assessment should be obtained at the **Follow-up visit or the Post-Study visit** ~~time of withdrawal from study~~.

Section 10.1 Permitted Medication(s)

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate Growth factors (*eg*, G-CSF) are not permitted during ~~dose escalation~~ **the DLT observation period** in Part 1, but may be allowable **beyond the**

DLT observation period in Part 1, in **the** PK-PD cohorts or in Part 2 ~~(expansion cohorts)~~ after discussion with the GSK medical monitor.

The use of anticoagulant and antiplatelet agents are permitted. However, prior to undergoing tumor biopsy, it is recommended that subjects be off agents such as coumadin or heparin for 5 days and then recheck labs prior to biopsy procedure. It is further recommended that subjects be off of NSAIDs for at least 48 hours. If institution guidelines require these agents be held longer than the recommended number of days/ hours, then follow institution guidelines. If there are risks of stopping these medications, contact the GSK Medical Monitor.

Section 10.2 Prohibited Medication(s)

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects should not receive other anticancer therapy (cytotoxic, surgery, tumor embolization, biologic, radiation, or hormone other than replacement) except where noted in the eligibility criteria while on treatment in this study

If corticosteroids are needed for chronic conditions, doses below 20 mg/day of prednisone or the equivalent are allowed. Corticosteroids exceeding this level are generally not allowed except as infusion pre-medication.

~~Chronic immunosuppressive therapies including daily steroid doses in excess of 20 mg/day of prednisone are prohibited while on treatment in this study.~~

Section 13.1.2, Title

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Part 2: Molecularly-Defined Tumor Histology Groups

Section 13.1.2 Molecularly-Defined Tumor Histology Groups

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For the ~~expansion cohorts~~ **groups** in Part 2, hypothesized response rates are provided in Section 13.2.2. A test that the response rate is less than or equal to the null hypothesis rate versus the response rate is greater than or equal to the alternative rate is being performed using the stopping rules provided. Descriptive statistics will be used to describe the observed response rates at the dose used in each of the ~~expansion cohorts~~**groups**.

Section 13.2.1 Part 1: Dose-Escalation Phase, 1st paragraph

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The total number of subjects in the Part 1 dose escalation will depend on the number of dose escalations needed **but the minimum number of subjects anticipated to complete dose escalation is 13 and**~~. However,~~ the anticipated number of subjects is approximately ~~31~~ **34** subjects. The selection of sample size ~~31~~**34** is based on the goal of fully exploring

available dose ranges for purposes of selecting an appropriate regimen(s) for Part 2. This will include a number of cohorts to establish an initial understanding of the dose - response relationship as well as to evaluate a range of PD biomarkers that may reveal the biological activity of GSK2849330. The initial cohort (1.4 mg/kg) will have 1 subject and cohorts 2 through ~~4~~ **5**will have 3 subjects in the dose escalation phase and up to an additional 3 subjects with evaluable pre- and on-treatment paired biopsies in each of these cohorts for the PK/PD cohorts. ~~Cohorts 5 through 7 will have up to 3 subjects with evaluable pre- and on-treatment paired biopsies in each cohort for the PK/PD cohorts~~. See Section 3.3 and ~~Table 2~~**Table 3** for additional details. The actual number of cohorts and subjects will depend in part on the observed toxicity and the PK and PD observed during the dose escalation.

Section 13.2.2, Title

REVISED TEXT

Part 2: ~~Expansion Cohort~~ **Molecularly-Defined Tumor Histology Groups**

Section 13.2.2 Part 2: Molecularly-Defined Tumor Histology Groups

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Once the recommended dose(s) and schedule(s) is/are confirmed from Part 1, at least 12 and up to 30 subjects per ~~arm~~ **group** will be enrolled at that dose(s) in ~~the expansion cohorts~~**Part 2**, guided by decision rules defined in Section 13.6.2. These guidelines are based on the predictive probabilities of success if enrollment were to continue to 30 subjects using the methodology of [Lee, 2008

The null hypothesis is:

H_0: $p \leq 10$%

H_A: $p \geq 30$%

Starting with a ~~cohort~~**group** of 12 subjects and allowing for a maximum sample size of 30 , this design will have a type I error rate (α) of 0.15and 94% power. ~~Cohort~~ **Group** enrollment is stopped early for futility if the predictive probability of success is less than 6%. The trial would not stop early for success. The Bayesian Prior was Beta (0.2, 0.8), a weak prior with a mean response rate of 20%. The ~~cohort~~ **group** outcome will be considered successful if the posterior probability of (P>0.10-observed data) is $\geq$ 80%. The futility boundary described in Section 13.6.2 was calculated based on the optimizing criterion of maximizing the power under the alternative hypothesis.

Under the null hypothesis, the expected sample size is 20 subjects and the probability of early termination is 77%. Under the alternative hypothesis, the expected sample size is 29 subjects and the probability of early termination is 5%.

Section 13.4.1: Analysis Populations

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The **All Treated Population** is defined as all subjects who receive at least one dose of GSK2849330. Safety will be evaluated based on this analysis population.

The Efficacy Population will consist of all subjects from the All Treated Population for whom at least one post-dose tumor assessment by CT scan has been performed.

The **PK Population** will consist of all subjects from the All Treated Population for whom at least one post-dose PK sample is obtained and analyzed.

Additional analysis populations may be defined in the RAP.

Section 13.6.2, Title

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough)~~

Part 2: ~~Expansion Cohort~~ **Molecularly-Defined Tumor Histology Groups**

Section 13.6.2 Part 2: Molecularly-Defined Tumor Histology Groups

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For each ~~cohort~~**of the groups** in Part 2 ~~the expansion cohorts~~**response data will be reviewed on an ongoing basis**~~., after~~ **After** the initial 12 subjects have enrolled at the recommended dose, ~~response data will be reviewed on an ongoing basis and~~ the number of responses observed will be compared with the stopping rules provided in the Table and Figure below.

Table 15 Stopping rules for each expansion group

Number of Subjects Enrolled	Stop for Futility if ≤ this number of responders is observed
12	0
16	1
22	2
27	3
30	4

Figure 3 Diagram of Stopping Rules for each Group

	Number of Responders					
Number of Subjects	0	1	2	3	4	5
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						
29						
30						

Section 13.7.1 Anti-Cancer Activity Analyses

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The ~~All Treated~~ **Efficacy Population** will be used for anti-cancer activity analyses. Since this is a Phase I study, anti-cancer activity will be evaluated based on clinical evidence and response criteria. Where appropriate, the lesion data will be listed for each subject. The percent change from baseline will be calculated for each subject and listed, along with their ORR, CR, PR, SD and PD according to standard RECIST 1.1 (See Appendix 5). mRECIST and irRc will be calculated and listed as applicable. Response data will be summarized by cohort or group. If data warrant, the response data will be summarized by dose level. Response-evaluable subjects are defined as subjects with a pre-dose and at least 1 post-dose disease assessment. Correlation analysis may be conducted to explore any relationship between the subject's tumor type specific markers and tumor response based on RECIST, version [1.1], mRECIST and irRc. Other measures of clinical benefit specific to the groups in Part 2 will be summarized by group as appropriate.

Full details will be specified in the RAP.

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Appendix 9 Management of Diarrhea

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances.

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea (Benson 2004). Presented in the sections below are the recommended guidelines for the management of diarrhea published by the ASCO panel (Benson 2004).

Early identification and intervention is critical for the optimal management of diarrhea. A subject's baseline bowel patterns should be established so that changes in patterns can be identified while subject is on treatment.

Subjects should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently subjects at high risk of diarrhea can be identified. Subjects should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that subjects keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations such as over the counter (OTC) medications, including herbal supplements, that may be useful in the evaluation of their diarrhea history.

Definitions

National Cancer Institute (NCI) guidelines define diarrhea compared to baseline (Table 19).

Table 31 Grading of Diarrhea

Adverse Event Grade	Diarrhea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living (ADL)
4	Life-threatening consequences; urgent intervention indicated
5	Death

Uncomplicated diarrhea is considered mild-to-moderate and defined as CTCAE Grade 1 or 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as any CTCAE Grade 3 or 4 diarrhea, or Grade 1 or 2 with one or more of the following signs or symptoms:

- **Moderate to severe abdominal cramping**
- **Nausea/vomiting ≥Grade 2**
- **Decreased performance status**
- **Fever**
- **Sepsis**
- **Neutropenia**
- **Frank bleeding (red blood in stool)**
- **Dehydration**

Management of Uncomplicated Mild to Moderate Diarrhea

Recommendation: Initial management of mild to moderate diarrhea should include dietary modifications (*e.g.*, eliminating all lactose-containing products and high osmolar dietary supplements), and the patient should be instructed to record the number of stools and report symptoms of life-threatening sequelae (*e.g.*, fever or dizziness on standing). Loperamide should be started at an initial dose of 4 mg

followed by 2 mg every 4 hours or after every unformed stool (not to exceed 16 mg/day).

If diarrhea resolves with loperamide, the patients should be instructed to continue dietary modifications and to gradually add solid foods to their diet. In the case of chemotherapy-induced diarrhea, patients may discontinue loperamide when they have been diarrhea-free for at least 12 hours.

If mild to moderate diarrhea persists for more than 24 hours, the dose of loperamide should be increased to 2 mg every 2 hours, and oral antibiotics may be started as prophylaxis for infection.

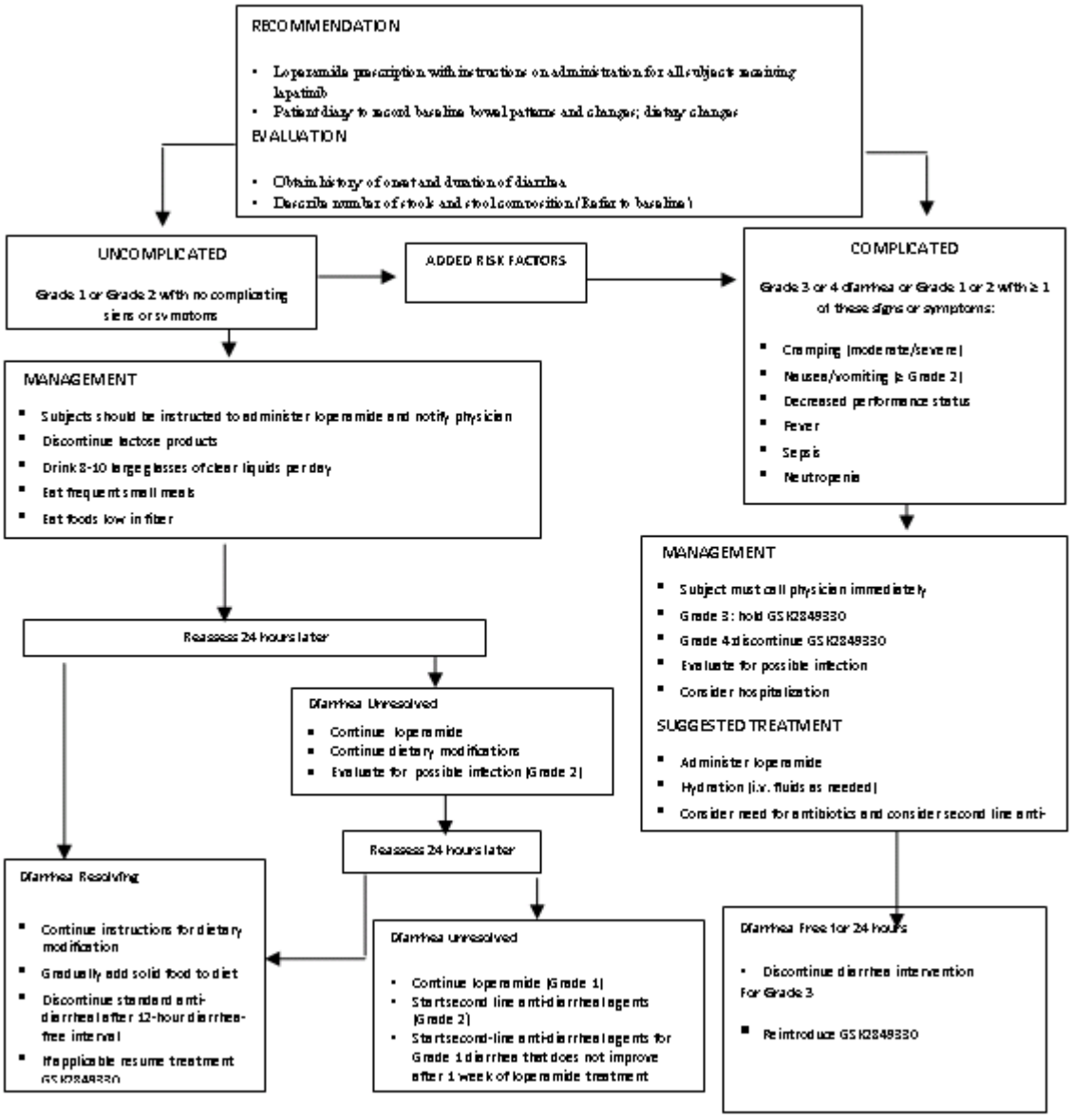
If mild to moderate chemotherapy-induced diarrhea has not resolved after 24 hours on high-dose loperamide (48 hours total treatment with loperamide), it should be discontinued and the patient should be started on a second-line antidiarrheal agent such as subcutaneous (SC) octreotide (100- to 150-μg starting dose, with dose escalation as needed) or other second-line agents (*e.g.*, oral budesonide or tincture of opium). In the case of chemotherapy-induced diarrhea, the patient should be seen in the physician's office or outpatient center for further evaluation, including complete stool and blood work-up. Stool work-up should include evaluation for pathogens. Fluids and electrolytes should be replaced as needed.

Aggressive Management of Complicated Cases

Recommendation: Aggressive management of complicated cases should involve IV fluids; octreotide at a starting dose of 100 to 150 g SC tid or IV (25 to 50 g/h) if the patient is severely dehydrated, with dose escalation up to 500 g until diarrhea is controlled, and administration of antibiotics (*e.g.*, fluoroquinolone). This may require admission to the hospital; for select patients, diarrhea may be managed with intensive home nursing or in a day hospital. Stool work-up (evaluation for blood, fecal leukocytes, *C difficile*, *Salmonella*, *Escherichia coli*, *Campylobacter*, and infectious colitis), complete blood count, and electrolyte profile should be performed. This may not be appropriate for radiotherapy-induced diarrhea. Any patient with chemotherapy-induced diarrhea who progresses to Grade 3 or 4 diarrhea after 24 or 48 hours on loperamide should also be treated as described above. Continue intervention as described until the patient has been diarrhea-free for 24 hours.

These recommendations for the aggressive management of complicated cases of chemotherapy-induced diarrhea are based on evidence that the GI syndrome is an indicator that the patient may be at serious risk for dehydration and/or infection and other potentially life-threatening complications. Moreover, loperamide, even at high-doses, may be less effective in patients with Grade 3 or 4 diarrhea. Therefore, it is appropriate to start immediate octreotide therapy (either SC or IV if the patient is already severely dehydrated) along with antibiotics.

Figure 2 Algorithm for the management of diarrhea



Amendment 2

Where the Amendment Applies

This amendment applies to all sites and countries.

Summary of Amendment Changes with Rationale

Typographical and formatting errors have been corrected and minor clarifications have been made throughout the document. These corrections have not been listed in this appendix, unless the correction changed the context or meaning of the text.

Inclusion Criteria

The inclusion criteria were modified for Molecularly Defined Tumor Histology Group 1 (melanoma), Group 2 (Gastric/GEJ), and Group 4 (NSCLC) in Part 2 to remove the statement that subjects would be eligibile for inclusion into the study if they had not received standard therapy when such therapy was not available to them commercially or via a clinical trial.

DLT Definition:

The definition of DLT for subjects with thrombocytopenia was expanded to include Grade 3 events of thrombocytopenia associated with bleeding in addition to all Grade 4 events.

Tumor Biopsy:

The statements regarding obtaining tumor biopsy samples have beem modified to include that all biopsies should be obtained from tumor easily accessible to biopsy using a procedure that is safe for the subject.

Total Blood Volume:

The total volume of blood to be collected within the first 30 days of participation has been modified to account for the increased frequency of PK sampling.

Time and Events Tables:

Inconsistencies were corrected and clarifications around visit and procedure windows were provided.

List of Specific Changes

Title Page, Authors

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

PPD ~~Projects Clinical Platforms and Sciences, RTP, USA~~
PPD Oncology Biomarkers, UP, USA

PPD	Biopharm Clinical Pharmacology, UM
PPD	Biopharm R&D, UM, USA
PPD	Global Oncology Data Sciences, RTP, USA
PPD	**Oncology R&D, USA**
PPD	**Clin Pharm, Mod & Sim, RTP, USA**
PPD	Oncology R&D, UP, USA
PPD	Oncology Clinical Statistics, UP, USA

LIST OF ABBREVIATIONS

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

FFPE	**Formalin fixed, paraffin-embedded**
qRT-PCR	**Quantitative real time polymerase chain reaction**

Protocol Synopsis, Study Rationale

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

GSK2849330 is a humanized ~~glycol-engineered~~ **glycoengineered** IgG1/IgG3 mAb with enhanced Fc-effector function potency, directed against HER3 (ErbB3), a signaling and drug resistance target expressed on a wide range of solid tumors. This FTIH, open-label, dose escalation study will assess the safety, PK, PD, and preliminary clinical effect of GSK2849330 in subjects with HER3-expressing or HER3 and NRG1 expressing solid tumors.

Protocol Synopsis, Number of Subjects

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Part 2: At least 4 molecularly defined tumor histology groups will be studied. A minimum of 12 and a maximum of 30 subjects will be enrolled in each of the groups. Futility criteria will be evaluated as data accrues, and enrollment in a group will be halted if futility criteria ~~conditions~~ are met for that group.

Protocol Synopsis, Inclusion/Exclusion Criteria- Pre-screening Inclusion Criteria Part 1

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

4. Sufficient archival tumor specimen is available for HER3 IHC analysis, or subject is willing to undergo a fresh tumor biopsy **(using a procedure that is safe for the subject)** for HER3 IHC analysis (see Section 7.6.1.1 for details).

Protocol Synopsis, Inclusion/Exclusion Criteria- Pre-screening Inclusion Criteria Part 2

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects with melanoma, gastric/gastroesophageal cancer, head and neck cancer, or NSCLC who appear to meet all inclusion and exclusion criteria may be pre-screened for the study provided that sufficient tumor specimen **either from archival Formalin-fixed paraffin-embedded (FFPE) tissue or tissue obtained by biopsy (using a procedure that is safe for the subject)** is available for analyzing HER3 by IHC or HER3 by IHC and NRG1 by RNA analysis.

Screening Inclusion Criteria for Parts 1 and 2

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. For subjects enrolled in Part 1: subjects must have tumors with documented HER3 expression (2+ or 3+) on the cell surface of the invasive component of the tumor ~~(either on archival tissue or fresh tumor biopsy)~~using an analytically validated IHC assay by central laboratory (see Section 7.6.1.1 for details). Subjects enrolled in Part 2 must meet inclusion criterion 9 listed below.
8. Subjects enrolled as part of the PK/PD cohort (Part 1) must agree to undergo pre- and on-treatment tumor biopsies, **using a procedure that is safe for the subject**

Protocol Synopsis, Inclusion Criteria for Part 2 ONLY

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

As listed above for Part 1, with the exception of criterion 3 which should be replaced with the following criterion 9 and the addition of criteria 10 and 11.

9. For Group 1: subjects with previously treated, unresectable stage III or IV melanoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor ~~(either on archival tumor or fresh tumor biopsy)~~using an analytically validated IHC assay by central laboratory.
    - Subjects must have received no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with BRAF V600 mutations who already received or were intolerant of prior BRAF inhibitor therapy may be included. ~~BRAF V600 inhibitor naïve subjects will be eligible if a BRAF inhibitor is not available to them commerciall or via a clinical trial.~~

- Subjects may be included if they had prior immune therapy, **or** were intolerant of prior immune therapy~~, or if such therapy is not available to them commercially or via a clinical trial.~~

For Group 2: Subjects with previously treated, unresectable stage III or IV gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor ~~(either on archival tumor or fresh tumor biopsy)~~ using an analytically validated IHC assay by central laboratory.

- Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
    - Subjects with HER2 positive disease may be included if they had already received prior anti-HER2 therapy, or were intolerant of prior anti-HER2 therapy, ~~or if such therapy is not available to them commercially or via a clinical trial~~.

For Group 3: Subjects with previously treated, unresectable stage III or IV cancers of the head and neck with documented HER3 expression **on the cell surface of the tumor** (≥1+) and NRG1 expression ~~on the cell surface of the tumor (either on archival tumor or frsh tumor biopsy)~~ using analytically validated assays by central laboratory.

- Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
- Subjects with locoregional recurrences amenable to resection/surgery or additional radiation are excluded.

For Group 4: Subjects with previously treated, unresectable stage III or IV NSCLC with documented HER3 expression **on the cell surface of the tumor** (≥1+) and NRG1 expression ~~on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy)~~ using analytically validated assays by central laboratory.

- Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
- Subjects with anaplastic lymphoma kinase (ALK) translocation who already received or were intolerant of prior anti-ALK therapy may be included. ~~Anti-ALK therapy naïve subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial~~.
- Subjects with EGFR mutation positive disease (e.g., exon 19 deletion and exon 21 L858R) who already received or were intolerant of prior EGFR inhibitors may be included. ~~EGFR inhibitor naïve subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.~~

Additional tumor histology groups predicted to be sensitive to the study drug based on emerging biomarkers (e.g.., HER3 mutations, NRG translocations) supported by preclinical or clinical data may be added based on emerging data.

10. Subjects must have at least one measurable lesion per RECIST v1.1.

    NOTE: If the only site of measurable disease has been previously irradiated, documented progression of disease and a 4-week interval since completion of radiotherapy is required.

    NOTE: In subjects with ≥1 measurable lesion, a measurable lesion may be biopsied at Screening and Day 15; however that lesion must not be selected as a target lesion for disease assessment.

11. Subjects must have disease amendable to biopsy **using a procedure that is safe for the subject,** and agree to undergo pre- and on-treatment tumor biopsies (until the participating centers receive written notification from the Sponsor that paired tumor biopsies are no longer required for any/all groups).

Section 1.2.1: GSK2849330 Background

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

GSK2849330 is a ~~glyco-engineered~~ **glycoengineered** antibody with enhanced potency for antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC causes tumor cell lysis upon binding of antibody to target, followed by engagement of cytotoxic T-cells and natural killer (NK) effector cells via their FcγRIIIA receptors. Perforin, granulysin and serine proteases released from cytoplasmic granules within cytotoxic T-cells and NK cells produce tumor cell lysis. CDC, considered one of the most powerful cell-killing mechanisms of antibodies [Walport, 2001], results from assembly of the 'membrane attack complex' that punches holes in the target cell membrane leading to tumor cell lysis. Compared with a wild-type antibody

Section 3.2: Pre-Screening

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects will be required to undergo pre-screening to determine if their tumor is HER3 expressing or HER3 and NRG1 expressing (details regarding HER3 and NRG1 expression requirements will be described in the SPM). Subjects with study eligible advanced solid tumors will sign a separate Informed Consent Form (ICF) to allow for pre-screening of archival tumor or tissue from fresh tumor biopsies **(obtained using a procedure that is safe for the subject)** for HER3 expression by IHC, or for HER3 expression by IHC and NRG1 expression by quantitative real-time polymerase chain reaction (qRT-PCR) assay.

Section 3.3: Part 1: Dose Escalation Phase

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects enrolled in the PK/PD cohorts must meet all of the relevant inclusion and exclusion criteria, have disease that is amenable to biopsy, and also agree to have pre- and on-treatment biopsies **(using a procedure that is safe for the subject)** in addition to

the other study procedures. Subjects will be enrolled in PK/PD cohorts in order to obtain evaluable pre- and on-treatment biopsy pairs per dose level (see SPM for additional details). Subjects who do not agree to, or who are unable to safely provide pre- and on-treatment biopsies in the PD expansion may be enrolled in dose escalation cohorts in Part 1 as they become available.

Section 3.3.1: Dose Limiting Toxicity

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

An event will be considered a DLT if it occurs within the first 4 weeks (28 days) of treatment, and meets one of the following criteria unless it can be clearly established that the event is unrelated to treatment:

a. Grade 3 or greater non-hematologic toxicity as described in Common National Cancer Institute-Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 [NCI, 2009] that cannot be controlled with routine supportive measures (e.g., antiemetics, antidiarrheals, antihistamines).

b. Grade 4 neutropenia lasting >5 days.

c. Febrile neutropenia, of any grade or duration as defined by NCI-CTCAE version 4.0 [NCI, 2009].

d. Grade 4 thrombocytopenia, **or Grade 3 thrombocytopenia associated with bleeding**.

e. Alanine aminotransferase (ALT) >3x upper limit of normal (ULN) with bilirubin >2x ULN.

f. Any Grade 2 or greater NCI-CTACAE version 4.0 [NCI, 2009] toxicity that in the judgment of the investigator and GSK Medical Monitor, would be considered dose-limiting.

g. Grade 3 or greater decrease in left ventricular ejection fraction (LVEF).

Section 3.4: Part 2: Molecularly Defined Tumor Histology Groups

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Part 2 can begin once the recommended dose and schedule is identified in Part 1. It is possible that more than one dose and/or schedule will be evaluated in Part 2 if available PK, PD and safety data suggest that multiple doses and schedules have desirable biologic activity or if an MTD cannot be established.

The selected dose level(s) will be evaluated in Part 2 for confirmation of safety and tolerability, as well as preliminary assessment of clinical benefit, in at least 4 molecularly-defined tumor histology groups of subjects with HER3 or HER3 and NRG1 expressing tumors Group 1 will include subjects with HER3- expressing melanoma. Group 2 will include subjects with HER3-expressing gastric cancer. Group 3 will include subjects with HER3 expressing and NRG1-expressing cancers of the head and neck. Group 4 will include subjects with HER3 expressing and NRG1-expressing NSCLC. All

subjects must have archival tissue available for HER3 and if required NRG1 testing or be willing to undergo a tumor biopsy **using a procedure that is safe for the subject**, to provide a sample for testing.

Each group will initially enroll 12 subjects with the option of expanding to a maximum of 30 subjects if futility criteria are not met using well established methodology of [Lee, 2008] (See Section 13.2.2 and Section 13.6.2 for additional details).

Subjects will be required to have disease amenable to biopsy and agree to pre-and on-treatment tumor biopsies, **using a procedure that is safe for the subject**. Pre-and on-treatment biopsies are mandatory for all subjects in all groups. GSK will closely monitor and evaluate the collection of evaluable biopsies and will notify the participating centers of any change to the collection requirements for any or all groups.

Section 3.5: Intra-subject Dose Escalation

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

A subject's dose level may be increased up to the highest dose level that has previously been confirmed by the investigator and GSK medical monitor as not exceeding the MTD. Intra-subject dose escalations will be allowed in both Part 1 and Part 2 (if multiple doses/regimens demonstrate a better PK profile or clinical activity) provided that the subject has completed **at minimum, the first 28 days of treatment with no sign or evidence of disease progression,** ~~at least 1 post-baseline efficacy assessment without~~ **no** toxicity greater than Grade 2 or the occurrence of significant AEs, and prior approval has been obtained from a GSK medical monitor. Subjects will be permitted to increase dose levels multiple times provided the above criteria are met. Any dose escalations must be agreed upon by the investigator and GSK medical monitor, and must be documented on an Intra-subject Dose Escalation Request Form (see the SPM) with copies maintained at the site and in the study files.

Section 3.6.3: Rationale for Dose: Maximum Proposed Dose:

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The maximum proposed dose of 30 mg/kg **for weekly, bi-weekly or every three week dosing** was selected based on PK-PD extrapolations which predict target engagement > 90% and tumor saturation should be achieved at or below this dose, and based on practical considerations (e.g., drug product supply and production capacity) Emerging PK, safety and tolerability data may cause the proposed maximum dose to be adjusted downward (see Section 3.3 for details of the N-CRM model assessment of safety data).

Preliminary Human Pharmacokinetic Profile

Arithmetic mean preliminary non-compartmental PK parameters **as of September 2014** are listed in Table 5 below for dose-escalation cohorts in this trial dosed GSK2849330 at 1.4 mg/kg, 3 mg/kg or, 10 mg/kg.

Table 5 Preliminary non-compartmental Pharmacokinetic Profile

Parameter	Unit	n	Treatment (mg/kg)	Estimate (CV%)
AUC(0,336)	h*µg/mL	1	1.4	3123
		3	3	8880 (25.7)
		3	10	28100 (27.8)
$t_{1/2}$ (24, 168)	hr	1/3	1.4	78.7
$t_{1/2}$ (24, 336)	hr	1/3	3	119
		3	10	134 (32.0)
C_{max}	µg/mL	1	1.4	29.8
		3	3	64.7 (30.2)
		3	10	234 (2.65)
t_{max}	hr	1	1.4	1
		3	3	1 [1-6][a]
		3	10	1[1-6] [a]

AUC = area under the concentration-time curve; Cmax = maximum observed concentration; CV = coefficient of variance; t1/2 = plasma elimination half-life; tmax = time to maximum observed concentration.
Preliminary non-compartmental PK analysis for subjects in dose-escalation cohorts.
a denotes median [range]

Preliminary population PK parameters based on nominal dose and PK sample time **as of September 2014** are listed in Table 6 below for dose-escalation cohorts at 1.4 mg/kg (n=1), 3 mg/kg (n=2) or, 10 mg/kg (n=2). The data are modelled according to a two compartment PK model with peripheral Target Mediated Drug Disposition. **The value of KM (concentration at half maximal saturation of peripheral target mediated drug disposition) is based on Biacore *in vitro* binding data together with an assumed 4/h rate of internalization and degradation based on semi-quantitative *in vitro* pulse chase experiment.** One subject was excluded from the 3 mg/kg cohort because the dose was delayed; and another subject was excluded from the 10 mg/kg cohort because the infusion was terminated early so the total dose of GSK849330 administered was uncertain.

Table 6 Preliminary Population PK Parameters

Parameter	Unit	Estimate	%RSE	%CV
CL	mL/h	11.4	39.1	31.3
V1	mL	**2830** ~~**2460**~~	6.64	
VM	µg/h	198	40.6	
KM	µg/mL	0.513		
Q	mL/h	79.0	19.1	
V2	mL	**3420** ~~**2500**~~	13.7	
D1	h	1		
SG1 (proportional)		0.0626	62.9	

The compartmental and non-compartmental model parameters suggest a catabolic half-life of (V1/CL)xln(2) = **172 hours** ~~150 hours~~. ~~Considering GSK2849330 as an IgG1-IgG3 fusion with Fc located in the IgG3 region, it is plausible that the elimination half-life is in accordance with the well-known fact that IgG3 elimination half-life is about 7 days (e.g., Stapleton, 2011 and references therein).~~

Predicted Effective Dose

The potential therapeutic dose range for GSK2849330 in humans was derived using available preclinical *in vitro* and *in vivo* PK and efficacy data. In addition, data from mouse *in vivo* CHL-1 xenograft efficacy studies were evaluated to predict the potential minimum clinically efficacious dose. PK/PD modeling of CHL-1 xenograft data in SCID mice suggests that anti-tumor efficacy (based on tumor growth curves) may be achieved with systemic plasma trough concentrations of GSK2849330 maintained at ≥ 20 µg/mL. The predicted human equivalent dose to achieve a similar trough concentration **in 90% of the population** is approximately ~~1.2mg/kg/wk~~ **1.4-3 mg/kg/wk**. This dose is also in line with that projected, based on *in vitro* potency data, to engage HER3 and inhibit signaling (approximately 0.9 to 5.6 mg/kg). It is anticipated that optimal anti-tumor activity will require full target engagement and that ADCC and CDC enhancements may further increase the anti-tumor activity of GSK2849330. However, it is also recognized that saturation of target throughout the tumor in the clinical setting may require doses higher than those projected based on preclinical extrapolations, due to factors in the tumor microenvironment such as vascular perfusion heterogeneity which may limit mAb intra-tumoral distribution. Recognizing these factors, the top proposed dose for

evaluation is 30 mg/kg, a dose which is also viewed as the highest dose feasible based on practical considerations.

A loading dose scenario is predicted to maintain an accumulated steady state trough concentration if the dosing interval is less than or equal to the elimination half-life. Accordingly, a 30 mg/kg weekly IV dose cohort has been added to the dose escalation portion of the study.

Section 5.2.1: Pre-screening Inclusion Criteria for Part 1

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects will be eligible for inclusion in pre-screening for the study (See Section 3.2) only if all of the following criteria apply:

1. Males and females ≥18 years of age (at the time consent is obtained).
2. Written informed consent provided.
3. Performance Status score of 0 or 1 according to the Eastern Cooperative Oncology Group (ECOG) scale (see Appendix 3).
4. Sufficient archival tumor specimen is available for HER3 IHC analysis, or subject is willing to undergo a fresh tumor biopsy **(using a procedure that is safe for the subject)** for HER3 IHC analysis (see Section 7.6.1.1 for details).

Section 5.2.2: Pre-Screening for Part 2

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Subjects with either melanoma, gastric/gastroesophageal cancer, head and neck cancer, or NSCLC who appear to meet all inclusion and exclusion criteria may be pre-screened for the study provided that sufficient tumor specimen, **either from archival FFPE tissue or tissue obtained by biopsy using a procedure that is safe for the subject** is available for analyzing HER3 by IHC or HER3 by IHC and NRG1 by RNA analysis.

Section 5.2.3: Screening Inclusion Criteria for Parts 1 and 2

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

3. For subjects enrolled in Part 1:subjects must have tumors with documented HER3 expression (2+ or 3+) on the cell surface of the invasive component of the tumor ~~(either on archival tissue or fresh tumor biopsy)~~using an analytically validated IHC assay by central laboratory (see Section 7.6.1.1 for details). Subjects enrolled in Part 2 must meet inclusion criterion 9 listed below.

8. Subjects enrolled as part of the PK/PD cohort (Part 1) must agree to undergo pre- and on-treatment tumor biopsies, **using a procedure that is safe for the subject**

Section 5.2.4: Inclusion Criteria for Part 2 ONLY

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

As listed above for Part 1, with the exception of criterion 3 which should be replaced with the following criterion 9 and the addition of criteria 10 and 11.

9. For Group 1: subjects with previously treated, unresectable stage III or IV melanoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor ~~(either on archival tumor or fresh tumor biopsy)~~ using an analytically validated IHC assay by central laboratory.
    - Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with BRAF V600 mutations who already received or were intolerant of prior BRAF inhibitor therapy may be included. ~~BRAF V600 inhibitor naïve subjects will be eligible if a BRAF inhibitor is not available to them commercially or via a clinical trial.~~
        - Subjects may be included if they had prior immune therapy, **or** were intolerant of prior immune therapy ~~or if such therapy is not available to them commercially or via a clinical trial~~.

    For Group 2: Subjects with previously treated, unresectable stage III or IV gastric or gastroesophageal junction (GEJ) adenocarcinoma with documented HER3 expression (3+) on the cell surface of the invasive component of the tumor ~~(either on archival tumor or fresh tumor biopsy)~~ using an analytically validated IHC assay by central laboratory.

- Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with HER2 positive disease may be included if they had prior anti-HER2 therapy or were intolerant of prior anti-HER2 therapy ~~or if such therapy is not available to them commercially or via a clinical trial.~~

    For Group 3: Subjects with previously treated, unresectable stage III or IV cancers of the head and neck with documented HER3 expression **on the cell surface of the tumor** (≥1+) and NRG1 expression ~~on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy)~~ using analytically validated assays by central laboratory.
        - Subjects must have no more than 3 prior lines of systemic therapy and have disease progression on or after last prior treatment (based on RECIST v1.1).
        - Subjects with locoregional recurrences amenable to definite surgery or additional radiation are excluded.

    For Group 4: Subjects with previously treated, unresectable stage III or IV NSCLC with documented HER3 expression **on the cell surface of the tumor** (≥1+) and NRG1 expression ~~on the cell surface of the tumor (either on archival tumor or fresh tumor biopsy)~~using analytically validated assays by central laboratory.

- Subjects must have no more than 3 prior lines of systemic regimens and have disease progression on or after last prior treatment (based on RECIST v1.1).
- Subjects with anaplastic lymphoma kinase (ALK) translocation who already received or were intolerant of prior anti-ALK therapy may be included. ~~Anti-ALK therapy naïve subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.~~
- Subjects with EGFR mutations (e.g., exon 19 deletion and exon 21 L858R) who have documented progression (based on RECIST 1.1) or who were intolerant of prior EGFR inhibitors may be included. ~~EGFR inhibitor naïve subjects will be eligible for the study if such a therapy is not available to them commercially or via a clinical trial.~~

Additional tumor histology groups predicted to be sensitive to the study drug based on biomarkers (e.g., HER3 mutations, NRG translocations) supported by preclinical or clinical data may be added based on emerging data.

10. Subjects must have at least one measurable lesion per RECIST v1.1.

    NOTE: If the only site of measurable disease has been previously irradiated, documented progression of disease and a 4-week interval since completion of radiotherapy is required.

    NOTE: In subjects with ≥ **>1** measurable lesion, a measurable lesion may be biopsied at Screening and Day 15; however that lesion must not be selected as a target lesion for disease assessment.

11. Subjects must have disease amendable to biopsy and agree to undergo pre- and on-treatment tumor biopsies **using a procedure that is safe for the subject** (until the participating centers receive written notification from the Sponsor that paired tumor biopsies are no longer required).

Section 7.0: Study Assessments and Procedures

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

The timing of each assessment is listed in the Time and Events Tables (Section 7.1). The timing and number of the planned study assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring for safety, PK, PD/biomarker, immunogenicity, imaging or other assessments. Changes in timing, addition, or removal of time points for any of the planned study assessments listed above must be approved and documented by GSK, but this will not constitute a protocol amendment. The institutional review board (IRB) or ethics committee (EC) will be informed of any safety issues that require alteration of the safety monitoring scheme. ~~No more than 200mL~~ **Up to approximately 350mL** of blood will be collected over a 30-day period, including any extra assessments that may be required.

Section 7.1: Time and Events Tables

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Table 7 Time and Events for Part 1 (Dose Escalation Cohorts, every 2 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)			Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 8	Day 15				
		-14 day window[3]		± 1 day window for each visit			± 3 day window for each visit	+ 7 day window	
Informed consent	X	X							
Archival tissue	X								
Tumor biopsy	X[4]	X[5]			X[6] pre-dose			X[7]	
Skin biopsy			X pre-dose		X pre-dose				
Baseline demographics	X	X							
Medical history	X	X	X						
Concurrent medication	Continuous								
Pregnancy test[8]		X[3]				X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]		X	X	Every 4 weeks	X	
Height (at screening only) and weight		X	X			X	Weight: Every 4 weeks	X	
ECOG		X	X[9]			X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X	X	X	Every 2 weeks	X	
12-lead ECG		X	X[10]		X	X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]	X	X	X	Every 2 weeks	X	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated						

	Pre-screening	**Screening**	**First Treatment Period (28 days)**					**Follow-up[1]**	**Post-study[2]**
			Day 1	**Day 8**	**Day 15**	**Day 29**	**Continuation Phase**		
		-14 day window[3]		**± 1 day window for each visit**			**± 3 day window for each visit**	**+ 7 day window**	
Urinalysis		X				X	Every 4 weeks	X	
ECHO[11]		X				X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	Every 12 weeks	X	X
Safety cytokines[20]			In the event of infusion reaction						
Circulating cell free DNA (cfDNA)			X pre-dose					X[7]	
Testosterone and LH[13]			X pre-dose			X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X	X	X		X[7]	
GSK2849330 IV infusion[15]			X		X	X	Every 2 weeks[15]		
AE assessment			Continuous						
Serum sample for Immunogenicity			X pre-dose	X		X	~~Every 12 weeks[16]~~	**X[16]**	X[16]
PGx sample			X pre-dose[17]						
Tumor markers [18]			X				Every 8 weeks		
Disease assessment[19]		X[3]					Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh pre- and on-treatment tumor biopsy is optional, but strongly encouraged for dose escalation cohorts; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.

6. Tumor biopsy is optional on Day 15 for dose escalation cohort subjects and required for the PK/PD cohorts. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected for subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to the start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. **If the screening visit was** completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1hour (± 15-minute window), and 6 hour (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. Additional PK samples will be collected at Day 8, Day 15, and Day 29. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year samples will be collected every 24 weeks. An additional PK sample will also be taken at the **Follow-up and** Post-study visits. Unless stated otherwise, on days of dosing sample will be drawn pre-dose. For the first subject in Cohort 1, additional PK samples will be taken at 24 hours (Day 2 [± 8-hours window]) and at 72 hours (Day 4 [± 24-hour window]) after the end of infusion of the first dose of GSK2849330.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For any subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2 week or every 3 week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules use the appropriate Time and Events Table as applicable.
16. After the first treatment period, immunogenicity samples will be collected every 12 weeks from the first dose within one year of treatment. If treatment continues after 1 year, samples will be collected every 24 weeks. An immunogenicity sample must be collected at **both the Follow up and** the Post-study visit.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.

20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For subjects who discontinue the study prior to disease progression, disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.

Table 8 Time and Events for Part 1 (Dose Escalation Cohorts, every week dosing schedule)

	Pre-screen	**Screen**	**First Treatment Period (28 days)**						**Day 29**	**Continuation Phase**	**Follow-up[1]**	**Post-study[2]**
			Day 1	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 22**				
		-14 day window[3]			**± 1 day window for each visit**					**±2 day window for each visit**	**+ 7 day window**	
Informed consent	X	X										
Archival tissue	X											
Tumor biopsy	X[4]	X[5]					X[6] pre-dose				X[7]	
Skin biopsy			X pre-dose				X pre-dose					
Baseline demographics	X	X										
Medical history	X	X	X									
Concurrent medication	Continuous											
Pregnancy test[8]		X[3]							X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X						X	Weight: Every 4 weeks	X	
ECOG		X	X[9]						X	Every 4 weeks	X	

	Pre-screen	Screen	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 2	Day 4	Day 8	Day 15	Day 22				
		-14 day window[3]			± 1 day window for each visit					±2 day window for each visit	+ 7 day window	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	X	X	Every week[22]	X	
12-lead ECG		X	X[10]				X		X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	X	Every week[22]	X	
Coagulation parameters: PT, INR, PTT		X	As clinically indicated									
Urinalysis		X							X	Every 4 weeks	X	
ECHO[11]		X							X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction									
Circulating cell free DNA (cfDNA)			X pre-dose								X[7]	
Testosterone and LH[13]			X pre-dose						X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X			X	X		X		X[7]	
GSK2849330 IV infusion[15]			X			X	X	X	X	Every week[15]		
AE assessment			Continuous									
Serum sample for Immunogenicity			X pre-dose								X[16]	X[16]
PGx sample			X pre-dose[17]									

	Pre-screen	Screen	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			Day 1	Day 2	Day 4	Day 8	Day 15	Day 22				
		-14 day window[3]			± 1 day window for each visit					±2 day window for each visit	+ 7 day window	
Tumor markers [18]			X							Every 8 weeks		
Disease assessment[19]		X[3]								Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh pre- and on-treatment tumor biopsy is optional, but strongly encouraged for dose escalation cohorts; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is optional on Day 15 for dose escalation cohort subjects and required for the PK/PD cohorts. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected for subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If **the screening visit** was completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window) and 24 hours (± 8-hour window) after the end of infusion. Pre-dose samples will also be collected on Day 4 **(± 1-day window)**, Day 8 **(± 1-day window)** and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and

every 12 weeks thereafter. If treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up and Post-study visits.

13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hr window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For any subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2 week or every 3 week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received Subsequent cohorts may receive different dosing schedules use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety biomarkers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. **For subjects who discontinue the study prior to disease progression, disease** assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

Table 9 Time and Events for Part 1 PK/PD Cohorts (every 2 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week								
			Day 1	Day 2	Day 4	Day 8	Day 15				
		- 14 day window[3]			± 1 day window for each visit				± 3 day window for each visit	+ 7 day window	
Informed consent	X	X									
Archival tissue	X										
Tumor biopsy	X[4]	X[5]					X[6] pre-dose			X[7]	
Skin biopsy			X pre-dose				X pre-dose				
Baseline demographics	X	X									
Medical history	X	X	X								
Concurrent Medication	Continuous									X	
Pregnancy test[8]		X[3]						X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X	X	Every 4 weeks	X	
Height (at screening only) and weight		X	X					X	Weight: Every 4 weeks	X	
ECOG		X	X[9]					X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	~~X~~			X	X	Every 2 weeks	X	
12-lead ECG		X	X[10]				X	X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	Every 2 weeks	X	
Coagulation parameters: PT, INR, PTT		X	As clinically indicated								

	Pre-screening	Screening	First Treatment Period (28 days)					Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15				
			Day 1	Day 2	Day 4	Day 8					
		- 14 day window[3]			**± 1 day window for each visit**				**± 3 day window for each visit**	**+ 7 day window**	
Urinalysis		X						X	Every 4 weeks	X	
ECHO[11]		X						X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction								
cfDNA			X pre-dose							X[7]	
Testosterone and LH[13]			X pre-dose					X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X		X	X	X		X[7]	
GSK2849330 IV infusion[15]			X				X	X[15]	Every 2 weeks[15]		
AE assessment	Continuous										
Serum sample for Immunogenicity			X pre-dose							X[16]	X[16]
PGx Sample[17]			X pre-dose								
Tumor markers [18]			X						Every 8 weeks		
Disease assessment[19]		X[3]							Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 15 dose.

7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. **If the screening visit was completed** within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected Day 1: pre-dose and at1 hour (± 15-minute window), 6 hours (± 1-hour window) and 24 hours **(± 8-hour window)** after the end of infusion. Pre-dose samples will also be collected on Day 4 **(± 1-day window),** Day 8 **(± 1-day window**)and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hour window), and 24 hours (Day 2 [± 8-hr window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will be collected at progression.
15. The study treatment dosing window is ± 3 days for subjects on an every 2 week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample will be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. For **subjects who discontinue the study prior to disease progression, disease** assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.

Table 10 Time and Events for Part 1 PK/PD Cohorts (every week dosing schedule)

	Pre-screening	Screening	First Treatment Period (28 days)								Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22	Day 29	Continuation Phase		
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]	± 1 day window for each visit							± 2 day window for each visit	+ 7 day window	
Informed consent	X	X										
Archival tissue	X											
Tumor biopsy	X[4]	X[5]					X[6] pre-dose				X[7]	
Skin biopsy			X pre-dose				X pre-dose					
Baseline demographics	X	X										
Medical history	X	X	X									
Concurrent Medication	Continuous										X	
Pregnancy test[8]		X[3]							X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]				X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X						X	Weight: Every 4 weeks	X	
ECOG		X	X[9]						X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	X	X	Every week[22]	X	
12-lead ECG		X	X[10]				X		X	Every 4 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	X	X	Every week[22]	X	

	Pre-screening	Screening	First Treatment Period (28 days)						Day 29	Continuation Phase	Follow-up[1]	Post-study[2]
			First Week				Day 15	Day 22				
			Day 1	Day 2	Day 4	Day 8						
		- 14 day window[3]			**± 1 day window for each visit**					**± 2 day window for each visit**	**+ 7 day window**	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated									
Urinalysis		X							X	Every 4 weeks	X	
ECHO[11]		X							X	Every 8 weeks	X	
PK (Blood)[12]			X	X	X	X	X	X	X	X[12]	X	X
Safety cytokines[20]			In the event of infusion reaction									
cfDNA			X pre-dose								X[7]	
Testosterone and LH[13]			X pre-dose						X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X		X	X		X		X[7]	
GSK2849330 IV infusion[15]			X			X[15]	X	X	X[15]	Every week[15]		
AE assessment	Continuous											
Serum sample for Immunogenicity			X pre-dose								X[16]	X[16]
PGx Sample[17]			X pre-dose									
Tumor markers [18]			X							Every 8 weeks		
Disease assessment[19]		X[3]								Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.

3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.
5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 15 dose.
7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. **If the screening visit was** completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of infusion. For subjects on a weekly dosing schedule, vital signs should be conducted weekly at each dosing visit in clinic.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected Day 1: pre-dose and at1 hour (± 15-minute window), 6 hours (-± 1-hr window) and 24 hours **(± 8-hour window)** after the end of infusion. Pre-dose samples will also be collected on Day 4**(± 1-day window),** Day 8 **(± 1-day window)** and weekly through Day 57 with additional 1-hour post-dose samples collected on Days 29 and 57. Pre-dose samples will also be collected on Day 71, Day 85 and every 12 weeks thereafter.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hour (± 1-hour window), and 24 housr(Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6 hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will be collected at progression.
15. For the subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days The study treatment dosing window is ± 3 days for subjects on an every 2 week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received. Subsequent cohorts may receive different dosing schedules. Use the appropriate Time and Events Table as applicable.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.

19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.
21. **For subjects who discontinue the study prior to disease** progression,disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

Table 11 Time and Events for Part 1 PK/PD Cohorts (every 3 week dosing schedule)

	Pre-screening	Screening	First Treatment Period (21 days)					Continuation Phase	Follow-up[1]	Post-study[2]
			First Week							
			Day 1	Day 2	Day 4	Day 8	Day 22			
		- 14 day window[3]			± 1 day window for each visit			± 3 day window for each visit	+7 day window	
Informed consent	X	X								
Archival tissue	X									
Tumor biopsy	X[4]	X[5]					X[6]pre-dose		X[7]	
Skin biopsy			X pre-dose				X pre-dose			
Baseline demographics	X	X								
Medical history	X	X	X							
Concurrent medication	Continuous								X	
Pregnancy test[8]		X[3]					X pre-dose	Every 3 weeks	X	X
Physical examination		X	X[9]				X	Every 3 weeks	X	
Height (at screening only) and weight		X	X				X	Weight: Every 3 weeks	X	
ECOG		X	X[9]				X	Every 3 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]			X	X	Every 3 weeks	X	

	Pre-screening	Screening	First Treatment Period (21 days)					Continuation Phase	Follow-up[1]	Post-study[2]
			First Week							
			Day 1	Day 2	Day 4	Day 8	Day 22			
		- 14 day window[3]			± 1 day window for each visit			± 3 day window for each visit	+7 day window	
12-lead ECG		X	X[10]				X	Every 3 weeks	X	
Hematology/Clinical Chemistry		X	X[9]			X	X	Every 3 weeks	X	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated							
Urinalysis		X					X	Every 3 weeks	X	
ECHO[11]		X					X	Every 9 weeks from day 22	X	
PK (Blood)[12]			X	X	X	X	X	Day 43 and every 12 weeks	X	X
Safety cytokines[20]			In the event of infusion reaction							
cfDNA			X pre-dose						X[7]	
Testosterone and LH[13]			X pre-dose				X	Every 9 weeks from day 22		
Whole blood/serum /cellular markers[14]			X	X		X	X	Day 43	X[7]	
GSK2849330 IV infusion[15]			X				X	Every 3 weeks[15]		
AE assessment	Continuous									
Serum sample for Immunogenicity			X pre-dose						X[16]	X[16]
PGx Sample[17]			X pre-dose							
Tumor markers [18]			X					Every 9 weeks		
Disease assessment[19]		X[3]						Every 9 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and disease assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.

5. Fresh tumor biopsy is required for the PK/PD cohort; if adequate tumor biopsy is obtained during pre-screening, then this does not need to be repeated. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 22 pre-dose for PK/PD cohort. Biopsy must be collected prior to administration of Day 22 dose.
7. Collected at progression. Tumor biopsy is optional and only required from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of childbearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 22 and every 3 weeks from Day 22 in the continuation phase of the study.
9. If **the screening visit was** completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. Collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion.
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 9 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. Additional PK samples will be collected at 24 hours (Day 2 [± 8-hr window]) and 72 hours (Day 4 [± 24-hour window]) after the end of infusion, and at Day 8 (± 1-day window), Day 22 (± 1-day window), and Day 43 (± 1-day window) after the first dose of GSK2849330. Additional PK samples will also be taken every 12 weeks from the first dose within 1 year of starting treatment and if treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will be collected at the Post-study visit. On days of dosing sample will be drawn pre-dose.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular marker. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), 6 hours (± 1-hourwindow), and 24 hours (Day 2 [± 8-hour window]) after the end of infusion. If a subject's duration of infusion is 3 hours or longer the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 22 and Day 43 for all cohorts. An additional blood sample should be collected at progression.
15. The study treatment dosing window is ± 3 days for an every 3-week dosing schedule. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received.
16. An immunogenicity sample will be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.

21. **For subjects who discontinue the study prior to disease** progression,disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.

Table 12 Time and Events for Part 2 Molecularly Defined Tumor Histology Groups

	Pre-Screen	Screen	First Treatment Period (28 days)				Day 29	Continuation Phase	Follow up[1]	Post study[2]
			Day 1	Day 8	Day 15	Day 22				
		-14 day window[3]		± 1 day window for each visit				± 2day window for each visit	+ 7 day window	
Informed consent	X	X								
Archival tissue	X									
Tumor biopsy	X[4]	X[5]			X[6] pre-dose				X[7]	
Baseline demographics	X	X								
Medical history	X	X	X							
Concurrent medication	Continuous									
Pregnancy test[8]		X[3]					X pre-dose	Every 4 weeks	X	X
Physical examination		X	X[9]		X		X	Every 4 weeks	X	
Height (at screening only) and weight		X	X				X	Weight: Every 4 weeks	X	
ECOG		X	X[9]				X	Every 4 weeks	X	
Vital signs (BP, pulse rate, Temperature)		X	X[10]	X[22]	X	X[22]	X	Every week[10,22]	X	
12-lead ECG		X	X[10]		X		X	Every 4 weeks	X[22]	
Hematology/Clinical Chemistry		X	X[9]	X[22]	X	X[22]	X	Every week[22]	X[22]	

	Pre-Screen	Screen	First Treatment Period (28 days)				Day 29	Continuation Phase	Follow up[1]	Post study[2]
			Day 1	Day 8	Day 15	Day 22				
		-14 day window[3]		± 1 day window for each visit				± 2day window for each visit	+ 7 day window	
Coagulation parameters: PT, INR, PTT		X	As Clinically Indicated							
Urinalysis		X					X	Every 4 weeks	X	
ECHO[11]		X					X	Every 8 weeks	X	
PK (Blood)[12]			X		X		X	X[12]	X	X
Safety cytokines[20]			In the event of an infusion reaction							
Circulating cell free DNA (cfDNA)			X pre-dose						X[7]	
Testosterone and LH[13]			X pre-dose				X	Every 8 weeks		
Whole blood/serum /cellular markers[14]			X	X[22]	X		X		X[7]	
GSK2849330 IV infusion[15]			X	X[22]	X	X[22]	X	Everyweek[15,22]		
AE assessment			Continuous							
Serum sample for Immunogenicity			X pre-dose						X[16]	X[16]
PGx sample			X pre-dose[17]							
Tumor markers [18]			X					Every 8 weeks		
Disease assessment[19]		X[3]						Every 8 weeks	X[21]	

1. The Follow-up visit should be approximately 28 days after the last dose of study treatment.
2. The Post-study visit should be at least 45 days or 5 half-lives (whichever is longer) after the last dose of study treatment.
3. Within 14 days prior to first dose except for pregnancy test (7 days) and Disease Assessment within 28 days prior to the first dose.
4. Separate pre-screening consent required for fresh biopsy and fresh biopsy is only collected at pre-screening if archived tissue is not available.

5. Fresh pre- and on-treatment tumor biopsy is required; if adequate fresh biopsy tumor tissue is acquired during pre-screening, then this does not need to be repeated during the screening period. Archival tumor tissue is not acceptable to serve as pre-treatment tumor tissue.
6. Tumor biopsy is required on Day 15. Biopsy must be collected prior to study treatment administration on Day 15 dose (pre-dose).
7. Collected at progression. Tumor biopsy is optional and only collected from subjects with disease progression on study treatment. The tumor specimen may be collected at any time after study treatment discontinuation, but must occur prior to start of any subsequent anticancer therapy.
8. Perform only in women of child-bearing potential. Serum pregnancy test should be conducted at the Screening, Follow-up, and Post-study visits. Urine pregnancy test should be conducted pre-dose on Day 29 and every 4 weeks from Day 29 in the continuation phase of the study.
9. If **the screening visit was** completed within 72 hours of the first dose, this assessment does not need to be repeated on Day 1.
10. For vitals: collect at pre-dose and at 1, 2, 4, and 6 hours after the start of the first infusion. For ECG: collect at pre-dose and 2 hours after the start of the first infusion
11. ECHO is preferred; however, if echocardiography is not available, or if reliable echocardiographic analysis of LVEF is unable to be obtained due to technical factors, a MUGA scan may be performed. Regardless, the method used at Baseline should be used for the remaining assessments in the study. Assessments should be performed more frequently than every 8 weeks if clinically indicated.
12. Blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window), after the end of infusion, and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and every 12 weeks thereafter. If treatment continues after 1 year, samples will be collected every 24 weeks. An additional PK sample will also be taken at the Follow-up or Post-study visits. Unless stated otherwise, on days of dosing sample will be drawn pre-dose.
13. To be conducted in male subjects only.
14. Whole blood for soluble markers from plasma, serum, and/or cellular markers. Blood samples will be collected on Day 1: pre-dose and at 1 hour (± 15-minute window) and 6 hours (± 1-hour window) after the end of infusion. If a subject's duration of infusion is 3 hours or longer, the 6-hour time point is optional. A pre-dose blood sample should be collected on Day 8, Day 15 and Day 29 for all cohorts. An additional sample will also be collected at progression.
15. For the subjects receiving a weekly dosing schedule, the study treatment dosing window is ± 2 days. The study treatment dosing window for all other dosing schedules (e.g., an every 2-week or every 3-week dosing schedule) is ± 3 days. If dosing does not occur on the intended day, all other assessments/subsequent visits should be changed accordingly relative to when the dose was received.
16. An immunogenicity sample must be collected at the Follow-up and Post-study visits.
17. It is preferred that the PGx sample be taken pre-dose on Day 1; however, it may be obtained anytime after informed consent has been given for PGx research.
18. See Section 7.8 and collect all tumor markers applicable for the subject's primary tumor type.
19. Confirmatory assessments will occur at least 4 weeks after assessments demonstrating CR or PR. Confirmatory assessments may be conducted at a subject's next regularly scheduled visit as appropriate.
20. A blood sample for select serum safety markers (including but not limited to TNF alpha, IL-6, and tryptase) should be drawn within 24 hours of suspected infusion-related reactions.

21. **For subjects who discontinue the study prior to disease** progression,disease assessment must be performed either at the Follow-up visit or at the Post-Study visit prior to the start of any subsequent anticancer therapy.
22. Assessments to be performed weekly while receiving weekly dosing and bi-weekly if switched to a bi-weekly dosing regimen.

Section 7.4: Pharmacokinetics

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

For the~~ expansion~~ **molecularly defined tumor histology groups** in Part 2, blood samples for analysis of GSK2849330 concentrations will be collected on Day 1: pre-dose and at 1 hour after the end of infusion; and pre-dose on Day 15, Day 29, Day 43, Day 57, Day 71, Day 85, and every 12 weeks thereafter.

Section 7.6.1.1: Tumor Tissue for Pre-Screening Assessments and Exploratory Research

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Tumor tissue taken from a metastatic site (preferably) or obtained at the time of primary cancer diagnosis (biopsy or from definitive surgery) is required to be submitted for analysis to one or more of the central laboratories, including Ventana Medical Systems to determine HER3 and NRG1 expression. If archival tumor tissue is not available, a fresh biopsy **using a procedure that is safe for the subject** is required for HER3 and NRG1 testing.

Section 7.6.1.2: Tumor Biopsies

REVISED TEXT (new text **bold and underlined**, deleted text in ~~strikethrough~~)

Every effort should be made to collect pre- and on-treatment tumor biopsies **using a procedure that is safe for the subject**. Image guidance has been shown to significantly increase the probability of success in obtaining tumor biopsies and is required for all percutaneous pre- and on-treatment biopsies in this study (with the exception of melanoma skin lesions or cutaneous metastases of other solid tumors).

Tumor biopsies are optional for subjects in the dose escalation cohorts, but strongly encouraged. All subjects enrolled in PK/PD cohorts in Part 1 and in each of the molecularly defined tumor histology groups in Part 2 must agree to pre and on-treatment tumor biopsies **(using a procedure that is safe for the subject)** for assessment of PD effect. GSK will closely monitor and evaluate the collection of evaluable biopsies and will notify the participating centers of any change to the collection requirements for any or all groups.

Tumor biopsies for PD analyses will be collected at the time points listed in the Time and Events Tables Section 7.1.

Tumor biopsies should be obtained upon disease progression, **using a procedure that is safe for the subject**, if the subject provides consent, and if the tumor is in a biopsy-accessible location. Once preliminary PK and PD data have been reviewed, the planned tumor biopsy collection times may be revised and provided to sites in writing. Changes in sample collection times will not constitute a protocol amendment