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Title:	Reporting and Analysis Plan for FGF117360, Multi-arm, Non-randomized, Open-Label Phase IB Study to Evaluate GSK3052230 in Combination with Paclitaxel and Carboplatin, or Docetaxel or as Single Agent in Subjects with Solid Malignancies and Deregulated FGF Pathway Signaling

Compound Number: GSK3052230 (FP-1039)

Effective Date: 01-MAR-2017

Description: The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol FGF117360. This RAP is intended to describe the safety, pharmacokinetics, pharmacodynamics, and anti-tumor activity analyses required for the study. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Subject: Oncology, Reporting and Analysis Plan, GSK3052230, Combination, Dose Escalation, NSCLC, Mesothelioma, predictive probability design

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Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CONMED	Concomitant Medication Dataset
CPMS	Clinical Pharmacology, Modeling and Simulation
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CTX	Anti-cancer Therapy Dataset
DISCHA1	Disease Characteristics Dataset
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Easter Cooperative Oncology Group
eCRF	Electronic Case Report Form
GHO	Global Health Outcomes
GSK	GlaxoSmithKline
HR	Hazard Ratio
IDMC	Independent Data Review Committee
IDSL	Integrated Data Standards Library
ITT	Intent to Treat
LCSS	Lung Cancer Symptom Score
LDH	Lactate Dehydrogenase
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Medical Affairs
MPM	Malignant Pleural Mesothelioma
NCI	National Cancer Institutes
NSCLC	Non-Small Cell Lung Cancer
ONCTTE	Oncology Time to Event Dataset
ONCSURV	Oncology Survival Dataset
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PGx	Pharmacogenetics
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
RAMOS	Registration and Medication Ordering System
RADIO	Radiotherapy Dataset
RAP	Reporting and Analysis Plan

RECIST	Response Evaluation Criteria in Solid Tumors
RESP2	Best Response Dataset
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
SRT	Safety Review Team
ULN	Upper Limit of Normal

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol FGF117360.

Protocol Revision Chronology:		
2013N165256_00	2013-APR-16	Original
2013N165256_01	2013-OCT-17	This amendment is a country-specific amendment for the UK. Stopping criteria based on QTc interval and contraceptive requirements have been revised.
2013N165256_02	2013-NOV-07	This amendment applies to all sites. Sponsor medical monitor information was updated, the inclusion criterion for FGFR gene amplification was modified, clarifications were made to the Time and Events Table, vital sign measurements, and permitted concomitant medications; and contraceptive requirements were corrected.
2013N165256_03	29-JAN-2014	This amendment changed Arm C of the protocol from GSK3052230 monotherapy of subjects with solid tumors to combination chemotherapy (GSK3052230 plus pemetrexed and cisplatin) of subjects with mesothelioma. Associated additions to the protocol include safety precautions for pemetrexed and cisplatin, use of modified RECIST for evaluation of clinical response, assessment of forced vital capacity. Patient reported outcomes using the Lung Cancer Symptom Scale (LCSS) was added for subjects with lung cancer and LCSS-meso for subjects with mesothelioma. Additional background and rationale were added. Stopping rules and sample size were modified. Translational research objectives were clarified.
2013N165256_04	2014-FEB-03	A minor correction to Amendment 3 was made on Page 24 to correct ototoxicity monitoring for consistency with the changes listed on page 114. As Amendment 3 was published prior to

Protocol Revision Chronology:		
		discovery of this inconsistency, the correction increases the document number from 03 to 04.
2013N165256_05	2017-FEB-17	This amendment added immunogenicity analyses section (Section 16) and added details for FGF biomarker analyses in the translational research section (Section 17). Clarifications were made to the definition and summary statistics for duration of dose delays. In addition, updates were made to the definition of study time periods.

This reporting and analysis plan (RAP) details all planned analyses required for a Clinical Study Report of study FGF117360. This is a phase IB study to characterize the safety and tolerability of GSK3052230 in combination with chemotherapy regimens and to assess the overall response rate (ORR) in each treatment arm. The study is composed of three separate treatment arms (A-C) with different study populations and chemotherapy regimens in combination with GSK3052230. GSK3052230 is combined with paclitaxel + carboplatin in previously untreated metastatic squamous NSCLC (Arm A), with docetaxel in metastatic squamous NSCLC that has progressed after 1 line of chemotherapy (Arm B), or with pemetrexed + cisplatin in malignant pleural mesothelioma (MPM) previously untreated with chemotherapy or investigational agents (Arm C). Within each study arm, expansion cohorts of 12-30 subjects are planned with futility rules based on a predictive probability design.

For further information on the study design, see the protocol (document number listed above).

The content of this RAP is based on the SOP and Information for Authors: Reporting and Analysis Plans (SOP_54838/GUI_137354) effective 23 March 2011.

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze of the study data. Interim analyses are detailed within Section 4.1, where applicable.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary

	Objectives	Endpoints
Primary	To characterize the safety and tolerability of GSK3052230 in combination with	Measurements used to evaluate safety and tolerability will include rate and severity of AEs, withdrawals due to AEs,

	Objectives	Endpoints
	chemotherapy regimens.	dose interruptions and reductions, treatment duration, and DLTs as well as change from baseline for the following: physical examinations, vital signs,:12-lead ECGs, ECHO, clinical laboratory tests.
	To determine the regimen of GSK3052230 in combination with chemotherapy for evaluation in future studies based on the maximum tolerated dose (or maximum feasible dose).	Maximum tolerated dose (MTD) or maximum feasible dose (MFD).
	To assess the overall response rate (ORR) in each treatment arm.	Best response defined as complete or partial response, stable disease or progressive disease according to RECIST 1.1 or modified RECIST (for MPM) ORR defined as the proportion of subjects with investigator-assessed confirmed complete response or partial response per RECIST 1.1 or modified RECIST (for MPM)

2.2. Secondary

	Objectives	Endpoints
Secondary	To assess progression free survival (PFS) for each treatment arm.	PFS is defined as the interval between first dose of GSK3052230 and the earliest date of disease progression or death due to any cause by investigator assessment per RECIST 1.1 or modified RECIST (for MPM)
Secondary	To characterize the population pharmacokinetics of GSK3052230 and identify important determinants of variability.	GSK3052230 population pharmacokinetic parameters such as clearance (CL) and volume of distribution (Vd), and relevant covariates which may influence exposure (e.g. age, weight, or disease related covariates).
Secondary	Assess improvement in Pulmonary Function Tests in Patients with MPM	Change from baseline in Forced Vital Capacity (FVC) in patients with MPM

2.3. Exploratory

	Objectives	Endpoints
Exploratory	To describe the kinetics of tumor growth in the presence of GSK3052230 for each treatment arm and investigate the relationship between tumor growth kinetics and clinical activity.	Tumor size over time, tumor growth rate constants, and time to tumor growth (TTG) predicted with the model parameters. Additional analysis will be performed utilizing volumetric analysis.
Exploratory	To identify biomarkers that may predict response or resistance.	Evaluate potential predictive/prognostic biomarkers (DNA, RNA, or protein) of response in circulation and/or in tumor.
Exploratory	To evaluate the pharmacodynamic response in circulation following treatment.	Changes in circulating biomarkers (eg, proteins) implicated in FGFR or disease biology signalling in pre and post dose blood samples.
Exploratory	To explore the relationship between PK, pharmacodynamic response, and clinical endpoints.	Predicted/observed exposure (AUC), trough concentrations ($C\tau$), or other PK endpoints as compared to pharmacodynamic and clinical endpoints.
Exploratory	To develop and validate a Fluorescence *in situ* hybridization (FISH) -based assay to measure *FGFR1* gene amplification status.	Association of *FGFR1* gene amplification with clinical response to support the development of an investigation use only test (IUO) and potential companion diagnostic for subject selection.
Exploratory	To investigate additional measures of FGF signaling pathway deregulation as potential predictive biomarkers for GSK3052230 in tissue.	Identification and validation of alternative measures of FGF signaling pathway deregulation retrospectively (eg, FGF2 overexpression) as predictive biomarkers for subject selection and potential development of a companion diagnostic
Exploratory	To evaluate changes in patient reported outcomes	Change from baseline and association with ORR in observer and patient assessed components of the Lung Cancer Symptom Scale (LCSS) and LCSS-meso
Pharmacogenetics	To investigate the relationship between genetic variants in the host DNA and the pharmacokinetics of GSK3052230 and/or the relationship between genetic variants in the host DNA and the efficacy, safety and tolerability of GSK3052230.	Refer to Section 20.2 Appendix 2

2.4. Statistical Hypotheses

No formal statistical hypotheses are being tested during the dose escalation portions of Arms A, B, and C. Analysis of the data obtained from the dose escalation parts of the study will be focused on comparison between dose cohorts and only descriptive methods will be used in analysis of the data.

Hypotheses for the dose expansion portions of the study are shown below for Arms A-C.

2.4.1. Arm A: GSK3052230 + Paclitaxel + Carboplatin

The null and alternative hypotheses for the overall response rate (p) are detailed below and are based on the most recent phase 3 evaluation of this regimen in NSCLC subjects including the squamous subset [Socinski, 2012].

The null hypothesis is:

H_0: $p \leq 25\%$

The alternative hypothesis is:

H_A:$p \geq 45\%$

2.4.2. Arm B: GSK3052230 + Docetaxel

The null and alternative hypotheses for the overall response rate (p) are detailed below and are based on previously published randomized phase 3 data in the 2nd line setting of metastatic NSCLC [Hanna, 2004].

The null hypothesis is:

H_0: $p \leq 10\%$

The alternative hypothesis is:

H_A:$p \geq 25\%$

2.4.3. Arm C: GSK3052230 + Pemetrexed + Cisplatin

The null and alternative hypotheses for the overall response rate (p) are detailed below and are based on previously published randomized phase 3 data in the 1st line setting of malignant pleural mesothelioma [Vogelzang, 2003].

The null hypothesis is:

H0: $p \leq 40\%$

The alternative hypothesis is:

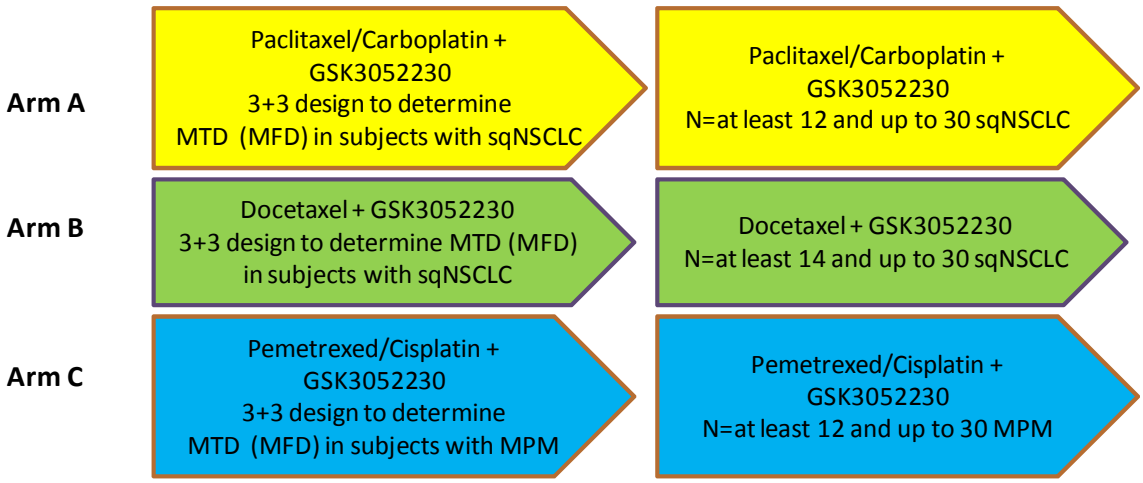
HA:$p \geq 60\%$

3. STUDY DESIGN

This study is a multi-arm, multicenter, non-randomized, parallel-group, uncontrolled, open-label Phase IB study designed to evaluate the safety, tolerability and preliminary activity of GSK3052230 in combination with paclitaxel + carboplatin (Arm A), in

combination with docetaxel (Arm B), or in combination with pemetrexed + cisplatin (Arm C). Treatment assignment information is captured on the eCRF's.

Figure 1 Study Schema



Dose escalation follows a 3+3 design as outlined in the Protocol Section 4.2 for determination of MTD (or MFD). In each arm, dose escalation will be followed by a cohort expansion with stopping rules for futility based on the methodology of Lee and Liu (Lee, 2008).

For Arm A, a total of at least 12 and up to 30 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 12 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm A are 0/12, 1/14, 2/17, 3/20, 4/22, 5/24, 6/26, 7/27, 8/28, 9/29, and 10/30 subjects and are shown in tabular format in Section 4.1. All available data will be considered in making enrollment decisions.

For Arm B, a total of at least 14 and up to 30 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 14 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm B are 0/14, 1/22, 2/26, 3/28, 4/29, and 5/30 subjects and are shown in tabular format in Section 4.1. All available data will be considered in making enrollment decisions.

For Arm C, a total of at least 12 and up to 30 subjects will be enrolled at the target dose to further evaluate safety and efficacy. After 12 subjects have been enrolled, the number of observed confirmed responses will guide further enrolment according to the stopping rules. The futility boundaries (inclusive) for ORR for Arm C are 2/12, 3/14, 4/16, 5/18, 6/20, 7/21, 8/23, 9/24, 10/25, 11/26, 12/27, 13/28, 14/29 and 15/30 subjects and are shown in tabular format in Section 4.1. All available data will be considered in making enrollment decisions.

4. PLANNED ANALYSES

As this is an open-label study, the treatment allocation (dose) is collected in the eCRF and this will be the treatment information used for interim and final analyses.

4.1. Analyses

4.1.1. Dose Escalation 3+3 Design

Review of preliminary safety and available pharmacokinetic data will be performed after completion of each dosing cohort. Preliminary safety data may include adverse events, changes in laboratory values and other safety parameters.

The GSK study team, in collaboration with study investigators, is to the review PK and safety data to support:

whether the dose should be escalated, and

the next dose level.

4.1.2. Interim Analysis for Futility/Efficacy Review

During the expansion cohorts of Arms A, B, and C regular interim analyses of the response data will be conducted in order to determine whether the futility criteria for stopping the Study Arm have been met. Study arms will not be stopped for efficacy based on success criteria.

Because subjects enrol at different times, not all subjects will have been on the study long enough to have single or multiple disease assessments. Since disease assessments are to be completed every 2 cycles during the first year of the study, we will set a cut-off date for inclusion in the interim analysis of subject first dose approximately 42 days (2 cycles) prior to the date the data are extracted. In addition, those subjects who are ongoing and were enrolled prior to the cut-off date but have not had a disease assessment will not be included in the interim analysis.

The study population used for decision-making at the interim analysis will be termed All Evaluable Subjects. This population may include subjects who were enrolled during dose escalation and who received the dose used in the expansion cohort as well as those subjects enrolled during the expansion cohort and who meet the cut-off date requirements as specified above. This will be the population for summaries of response data. The population of all subjects that have been enrolled at the time of the interim analysis will be termed the All Treated Subjects population. This will be the population for listings of data.

A listing of subject responses over time will be produced. The listing will show the responses observed at each timepoint for each subject along with the best confirmed response. The definition of confirmed response is provided in the protocol for FGF117360, Section 7.4. The study population for this display will be All Treated Subjects.

In addition, a listing of subject best response by first dose date will be provided using the All Treated Subjects Population. This listing will be sorted by date of first dose and will show whether or not each subject is ongoing, whether the subject has had at least one disease assessment, whether the subject is evaluable for the interim analysis, and best confirmed and unconfirmed response.

Summaries of best response (confirmed) and best response (unconfirmed) will be provided so that the study team can compare the study data to the stopping rules for futility and to the success rules. The population for these displays will be All Evaluable Subjects.

A waterfall plot of response by subject as well as a bar graph of time on treatment for each subject will be produced. Volumetric data may also be examined.

Stopping boundaries are based on the number of confirmed responses out of the number of evaluated subjects; however, subjects who are ongoing in the trial at the time of an interim analysis with either a non-confirmed response or stable disease may eventually have a confirmed response. Therefore, the total number of subjects with confirmed or unconfirmed responses plus those who are ongoing with stable disease should be compared to the futility boundary to prevent stopping the trial for futility before all potential confirmed responses are fully realized. Because this represents the best-case scenario, if this count is within the futility region, the study should be stopped.

These rules are considered guidelines for decision-making and the totality of the data will be considered by the team when making a decision to stop the study.

A high-level summary of the decision from the interim analysis will be provided in meeting minutes after the team reviews the data.

Table 1 Stopping Rules for Arm A: GSK3052230 + Paclitaxel + Carboplatin

Number of Evaluable Subjects	≤ This Number of Objective Responses to Stop Early for Futility
12	0
13	0
14	1
15	1
16	1
17	2
18	2
19	2
20	3
21	3
22	4
23	4
24	5
25	5
26	6
27	7
28	8
29	9
30	10

Table 2 Stopping Rules for Arm B: GSK3052230 + Docetaxel

Number of Evaluable Subjects	≤ This Number of Objective Responses to Stop Early for Futility
14	0
15	0
16	0
17	0
18	0
19	0
20	0
21	0
22	1
23	1
24	1
25	1
26	2
27	2
28	3
29	4
30	5

Table 3 Stopping Rules for Arm C: GSK3052230 + Pemetrexed + Cisplatin

Number of Evaluable Subjects	≤ This Number of Objective Responses to Stop Early for Futility
12	2
13	2
14	3
15	3
16	4
17	4
18	5
19	5
20	6
21	7
22	7
23	8
24	9
25	10
26	11
27	12
28	13
29	14
30	15

4.2. Final Analyses

Final analyses will be performed after all subjects have either permanently discontinued study treatment or have been enrolled in the study at least 12 months (starting from the first day of GSK3052230) and the final study database is frozen.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

The sample sizes for the dose escalation portion of Arms A-C are not determined based on hypothesis testing considerations. The number of subjects will be determined based in part on the number of cohorts required to define the MTD (or MFD).

The sample size for the expansion cohorts for Arms A-C is based on the methodology of Lee and Liu and the null and alternative hypotheses given in Section 2.4.

5.1.1. Arm A: GSK3052230 + Paclitaxel + Carboplatin

Starting with a cohort of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.11 and 86% power. The trial is stopped early

for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.3, 0.7), a relatively non-informative prior with a mean response rate of 30%. Under the null hypothesis, the expected sample size is 24.2 subjects and probability of early termination is 83.5%. Under the alternative hypothesis, the expected sample size is 29.7 subjects and the probability of early termination is 9%.

5.1.2. Arm B: GSK3052230 + Docetaxel

Starting with a cohort of 14 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.07 and 79% power. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0.15, 0.85), a relatively non-informative prior with a mean response rate of 15%. Under the null hypothesis, the expected sample size is 24.0 subjects and probability of early termination is 84.5%. Under the alternative hypothesis, the expected sample size is 29.5 subjects and the probability of early termination is 12.2%.

5.1.3. Arm C: GSK3052230 + Pemetrexed + Cisplatin

Starting with a cohort of 12 subjects and allowing for a maximum sample size of 30, this design will have a type I error rate (α) of 0.10 and 82% power. The trial is stopped early for futility if the predictive probability of success is less than 0.1%. The Bayesian prior used in determining the design was Beta (0. 5, 0.5), a relatively non-informative prior with a mean response rate of 50%. Under the null hypothesis, the expected sample size is 23.1 subjects and probability of early termination is 86.4%. Under the alternative hypothesis, the expected sample size is 29.5 subjects and the probability of early termination is 13.7%.

5.2. Sample Size Sensitivity

No sample size sensitivity was performed.

5.3. Sample Size Re-estimation

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

6. ANALYSIS POPULATIONS

6.1. All Treated Subjects

The All Treated Subjects (ATS) population will be comprised of all subjects who receive at least one dose of study treatment.

6.2. All Evaluable Subjects Population

The study population used for decision-making at the interim analyses during the dose expansion cohorts of the study arms will be termed the All Evaluable Subjects Population.

Since disease assessments are to be completed every 2 cycles during the first year of the study, we will set a cut-off date for inclusion in the All Evaluable Subjects Population of subject first dose approximately 42 days (2 cycles) prior to the date the data are extracted for the interim analysis. In addition, those subjects who are ongoing and were enrolled prior to the cut-off date but have not had a disease assessment will not be included in the interim analysis (e.g. if they are late having their first scan or the scan data has not yet been received).

6.3. Pharmacokinetic Population

The Pharmacokinetic Population will consist of all subjects in the All Treated Subject Population for whom a blood sample for pharmacokinetics is obtained and analyzed.

6.4. Pharmacodynamic Population

The Pharmacodynamic Population will consist of all subjects in the All Treated Subjects Population for whom a biomarker sample was obtained and analyzed.

6.5. Assay Validation Population

The Assay Validation Population is defined as all subjects who were consented, screened for the study (regardless if the subject met eligibility requirements for study enrolment) and whose tissue was assayed by the central laboratory for *FGFR1* amplification. Data from this population may be used for future validation of the assay.

6.6. Analysis Datasets

The dataset used for summaries of response data during the dose expansion cohort interim analyses will be comprised of the All Evaluable Subjects Population.

The primary dataset for dose escalation cohort reviews, for review of safety data and listings of response data at interim analyses during the dose expansion cohort, and for the final analysis of efficacy and safety data will be the All Treated Subjects Population.

The primary dataset for the analysis of PK data will be comprised of the Pharmacokinetic Population.

The primary dataset for analysis of biomarker data, including potential predictive/prognostic biomarkers (DNA, RNA, or protein) of response in circulation and/or in tumor will be the Pharmacodynamic dataset.

The primary dataset for analysis of *FGFR1* gene amplification data to support the IUO application and potential development of a companion diagnostic will be comprised of the Assay Validation Population.

7. TREATMENT COMPARISONS

There will be no formal statistical comparison of dose groups. Comparisons of safety and PK data across dose groups will be made using descriptive statistics, separately for each Study Arm.

For analysis of the overall response rate (ORR) for each study arm, ORR data from dose expansion cohorts are compared against historical control rates using the hypotheses specified in Section 2.4. The type I error rate and power for this comparison is provided by study arm in Section 5.1.

7.1. Data Display Treatment and Other Subgroup Descriptors

The following treatment descriptor formats will be used on all applicable displays. Actual doses should be used in data displays. An example is given for each study arm:

Study Arm	Description	Data Display Example	Order of Treatment Groups
A	GSK3052230 + Paclitaxel + Carboplatin	5 mg/kg GSK3052230 + 200 mg/m2 Paclitaxel + AUC6 Carboplatin	Sort by dose of GSK3052230, then by dose of Paclitaxel, then by dose of Carboplatin
B	GSK3052230 + Docetaxel	5 mg/kg GSK3052230 + 75 mg/m2 Docetaxel	Sort by dose of GSK3052230 then by dose of Docetaxel
C	GSK3052230 + Pemetrexed + Cisplatin	10 mg/kg GSK3052230 + 500mg/m2 Pemetrexed + 75 mg/m2 Cisplatin	Sort by dose of GSK3052230, then by dose of Pemetrexed, then by dose of Cisplatin

Note: When there is not space for the entire title, the data display column header may read e.g. “Treatment (GSK3052230,Paclitaxel,Carboplatin)” and the dose description may be shortened to e.g. “5mg/kg,200mg/m2,AUC6”.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis datasets will be created according to GSK Integrated Data Standards Library (IDSL) for interim analyses and according to CDISC/ADaM standards for final reporting. Data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards for both interim and final analyses. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

The currently supported versions of SAS and Tibco Spotfire Clinical Graphics (TSCG) software will be used to perform all data analyses, generate tables, figures, and listings.

All data in the database will be presented in by-subject data listings.

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. There will be no imputation for missing data.

Unless otherwise stated, all listings will be sorted by study part, treatment group, center ID, subject number, cycle, cycle day, and then by visit date and time, if applicable.

Unless otherwise stated, continuous variables will be summarized with n, mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

Data from Study Arms A-C will be reported separately.

Generally, summaries for each Study Arm will be produced by study treatment with pooling over the dose escalation and dose expansion portions of the Study Arm. Certain displays may be created using only data from the dose escalation or dose expansion portion of the Study Arm or using only data from subjects who received the RP2D.

All laboratory data will be presented in GSK's standard units for reporting.

"Worst-case post-baseline" values will be derived using scheduled and unscheduled visits.

Planned times relative to study drug dosing will be used in all tables and summary figures.

Generally, only pre-specified planned times will be used in the summaries, statistical analyses and calculations of any derived parameters and unscheduled readings will be listed. However, both unscheduled and scheduled readings will be included in the computation of maximum toxicity and in post-baseline shifts displays for labs and in any summary or listing of Potential Clinical Importance (PCI) values for vitals and ECG readings.

Actual, rather than planned, sampling times will be used in the derivation of PK parameters and in the individual concentration-time plots and listing of PK concentration data. Planned times will be used in the descriptive summaries and in mean and median plots. Concentration-time data will be listed according to actual sampling times relative to dosing time.

Assessment windows will not be defined for the purpose of classifying measurements obtained outside scheduled assessment times.

Deviations from the analyses in the RAP will be identified in the CSR.

8.1. Multicenter Studies

Data from all participating centers will be pooled prior to analysis. It is anticipated that subject accrual will be spread thinly across centers. Summaries of data by center will not, therefore, be provided.

8.2. Other Strata and Covariates

In all efficacy analyses, there are no formal plans for any stratification. There are no formal plans for investigating any covariates.

8.3. Examination of Subgroups

There are no formal plans for examining subgroups.

8.4. Multiple Comparisons and Multiplicity

There will be no adjustment of Type I error rates for multiple comparisons.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

Because study treatment is dependent on the study endpoints (e.g., progression, i.e. not a fixed treatment duration), the length of treatment for each subject will depend on the efficacy and toxicity of the treatment, so the duration of treatment will vary across subjects. Similarly the duration of follow up will also vary. All available data will be analyzed using suitable statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing data. For endpoints which determine the percentage of responders, subjects with unknown/not evaluable or missing best overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

In the event that the study is terminated, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for adverse events (AE)s and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than what is described in Section 9.2 for partial dates and for missing exposure end dates.

9.2. Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of core standard algorithms and standard Oncology algorithms. The analysis dataset

specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

9.2.1. Reference dates

There are two reference dates:

- The date of screening is the reference date for determination of age. This date is used as a reference for age because age is an eligibility requirement.

- The treatment start date is the safety reference date as well as the efficacy reference date. The treatment start date is defined as the date of first dose of GSK3052230 study treatment. It will be used to calculate study day for safety measures, to calculate study day for response measures, for calculation of treatment duration, and for baseline characteristic measures such as time since initial diagnosis.

9.2.2. Study Day for Safety and Efficacy Measures

If the date of interest occurs on or after the safety reference date then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

9.2.3. Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.
- If the reference date is before the event date then the elapsed time is the reference date minus the event date.

When reporting time to event (TTE) durations such as PFS in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

For converting all other durations (e.g., duration of adverse events, duration of exposure, age to weeks, months or years use the following:

- To report the duration in weeks divide the number of days by 7.
- To report the duration in months use:

(YEAR(stopdate + 1) - YEAR(startdate)) * 12 + (MONTH(stopdate + 1) - month(startdate) - 1) + (DAY(stopdate + 1) > = DAY(startdate))

- To report the duration in years use:

  intck('year', startdate, stopdate + 1) - (month(stopdate + 1) < month(startdate) or (month(stopdate + 1) = month(startdate) and day(stopdate + 1) < day(startdate)))

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

9.2.4. Imputation of Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.

With the exception of new anti-cancer start date on the Oncology time to event analysis dataset and exposure end date on the Exposure analysis dataset, imputed dates will also not be stored on datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for ‘slotting’ data to study time periods (see Section 9.3) or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

Adverse Events (AE):

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. • Else set start date = study treatment start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. • Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date		• No imputation for partial end dates will be performed

Anti-Cancer Therapy and Radiotherapy:

Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g., to calculate duration), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment anti-cancer therapy and radiotherapy start dates may be imputed to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not all anti-cancer therapy and radiotherapy start dates) will be stored on appropriate efficacy datasets. Imputed partial dates will not be used to derive time since most recent prior therapy. In addition, the cancer therapy treatment status variable, and not any variables that use imputed partial dates, will be used to differentiate prior and follow-up anti-cancer therapy and radiotherapy.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy Radiotherapy	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial date contains a year only set to January 1st.
		day	• If partial date contains a month and year set to the 1st of the month.
	End Date		• No imputation for partial end dates will be performed

Surgery:

The date of surgery or procedure is generally not imputed. If the date of surgery or procedure needs to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment surgery or procedure dates maybe imputed (where applicable) to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not specific surgery or procedure date) will be stored on appropriate efficacy datasets. The category for surgical procedure variable, and not any variables that use imputed partial dates, will be used to differentiate prior, on, and follow-up surgical procedure data. The derived time in relation to treatment variables are not needed for reporting of data because the category for surgical procedure variable can be used. Therefore, imputed dates are not needed for derivation of time in relation to treatment.

Dataset	Missing Element	Rule
Surgical Procedures	day, month, and year	• No Imputation for completely missing dates
	day, month	• If partial date contains a year only set to January 1st.
	day	• If partial date contains a month and year set to the 1st of the month

Concomitant Medication and Blood and Blood Supportive Care Products:

Start and end dates may be imputed for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but should not be permanently stored

in the analysis datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

Dataset	Date	Missing Element	Rule
Concomitant Medication Blood and Blood Supportive Care Products	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. ▪ Else set start date = study treatment start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. ▪ Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact (MSTONE.LCONTDT).

Time to Event and Overall Response:

Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e. start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed date(s) will not be stored on the anti-cancer therapy, radiotherapy, or surgical procedure datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures datasets:

Dataset	**Date**	**Missing Element**	**Rule**
Anti-Cancer Therapy Where applicable: Radiotherapy Surgical Procedures	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• No imputation for missing day and month (note the eCRF should only allow for missing day)
		Day	• If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study treatment+1, last day of month). • If partial date falls in the same month as the subject's last assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month.
	End Date		• No imputation for partial end dates will be performed

The date of new anti-cancer therapy is derived as the earliest date of new anti-cancer therapy (e.g., chemotherapy), radiotherapy (where applicable), or cancer related surgical procedure (where applicable) and will include imputed dates. If the date of new anti-cancer therapy is an imputed date, then the date of new anti-cancer therapy flag variable is assigned the value of 'D' to indicate that the day portion of the date is imputed (following ADaM convention).

As multiple dates are used to derive the date of new anti-cancer therapy, ensure that the date of new anti-cancer therapy flag is only set to 'D' if the derived date is imputed. For example, if the date of new radiotherapy is imputed but the date of new anti-cancer therapy is prior to date of new radiotherapy and the new anti-cancer therapy date is not a partial date then the flag should be set to missing as the date used for the new anti-cancer therapy is not an imputed date.

9.2.5. Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the first study GSK3052230 treatment dose date. For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date. If there are no central labs collected for a subject and lab test prior to or on the first dose of study treatment, the most recent, non-missing value from a local laboratory prior to or on the first dose of study treatment will be defined as the baseline value.

For subjects who did not receive GSK3052230 treatment during the study, baseline will be defined as the latest, non-missing collected value.

9.2.6. Change from baseline

Change from baseline will be presented for safety data as described in Section 12.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

9.2.7. Multiple Assessments

All data will be reported according to the nominal visit date for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in the display sections that report worst- case post-baseline.

If multiple assessments are reported on the same date for the same scheduled planned time, then the mean of multiple measurements reported for the same date will be

analyzed, with the exception of laboratory data reported from both central and local laboratories. If laboratory data is reported from both central and local laboratories with the same date, then the central laboratory data will be analyzed to provide consistency with measurements from other subjects.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

9.2.8. Actual Treatment

The subjects' actual treatment will be derived from exposure data. If a subject's actual treatment is the same as the assigned treatment, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

9.2.9. Treatment Cycle

In order to differentiate cycle variables based on the "assessment" cycle (timeslicing/eCRF collected) versus actual treatment cycle variables based on exposure cycle start dates, treatment cycle, treatment cycle description, day with treatment cycle, day of start within treatment cycle, and day of end within treatment cycle, as appropriate, will be added to adverse events, ECG, laboratory, and vital sign analysis datasets.

Treatment cycle:

- For non-planned visits/assessments select the cycle record for each subject where the dataset date variable is greater than or equal to cycle start date and less than or equal to cycle end date.
- For planned visits/assessments where Day 1 assessments are assumed to be done prior to dosing, add 1 to the cycle start date and cycle end date from the cycle dataset. For each subject, select the cycle record where the dataset date variable is greater than or equal to the cycle start date and less than or equal to the cycle end date.

Treatment cycle description:

- Set treatment cycle description to the cycle dataset cycle description where the cycle dataset cycle is equal to the dataset treatment cycle.

Day within treatment cycle:

- For each subject, dataset date variable minus the cycle start date from the cycle dataset + 1 where the dataset date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

Day of start within treatment cycle:

- For each subject, dataset start date variable minus the cycle start date from the cycle dataset + 1 where the dataset start date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

Day of end within treatment cycle:

- For each subject, dataset end date variable minus the cycle start date from the cycle dataset + 1 where the dataset end date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

9.2.10. Extended Loss to Follow-up or Extended Time without an Adequate Assessment

As the assessment schedule changes through the course of the protocol (i.e. every 2 cycles for 1 year then every 4 cycles thereafter), the following rules will be used for identifying extended loss to follow up or extended time without an adequate assessment(i.e. two or more missed assessments) .

- If death or PD is on or prior to day 343 (16 cycles + 7 day window), then a subject will be identified as an extended loss to follow up if the subject did not have an adequate disease assessment during the time period of 91 days (4 cycles + 7 day window) prior to death or PD;
- Else if death or PD is after day 343 (16 cycles + 7 day window) and on or prior to day 434 (16 cycles + 4 cycles + 14 day window), then a subject will be identified as an extended loss to follow up if the subject did not have an adequate disease assessment during the time period of 140 days (2 cycles+ 4 cycles + 14 day window) prior to death or PD.
- Else if death or PD is after day 434 (16 cycles + 4 cycles + 14 day window), then a subject will be identified as an extended loss to follow up if the subject did not have an adequate disease assessment during the time period of 182 days (8 cycles + 14 day window) prior to death or PD.

9.2.11. Date Associated with Response

For each disease assessment after baseline, determine a date associated with the response. For complete response (CR) and partial response (PR), assign to the latest date within the disease assessments. For stable disease (SD), Non-CR/Non-PD or Not Evaluable, assign to the earliest date within the disease assessments. For progressive disease (PD), assign to the earliest assessment date associated with the progression.

9.2.12. Cardiac Scan Modalities (ECHO/MUGA)

The same modality (ECHO or MUGA) for determining cardiac scan data (e.g., left ventricular ejection fraction (LVEF)) should be used to follow a subject throughout the study. The absolute change from baseline values will not be calculated for any subjects

where the post-baseline value was determined by a cardiac scan modality that is different than the one used to determine baseline value.

9.2.13. Derived and Transformed Variables

Progression-free survival

See Section 11 for details on analyses for progression-free survival, including censoring rules.

Pharmacokinetic Parameters

See Section 14 for details on the derivation of PK parameters.

For the purposes of calculating summary statistics and for statistical analysis, all PK parameters with the exception of tmax and %AUCex will be $\log_e$ transformed.

Between-subject coefficient of variation (CVb%) will be calculated by the following methods, where SD is the standard deviation of the PK parameter data, calculated using either the raw data (untransformed) or the natural logarithm of the raw data (transformed).

Untransformed Data: 100 * (SD/Mean)

Transformed Data: 100 * (square root[exp(SD2)-1])

ECG Corrected QT Intervals

An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals will be used and these values will be input into the eCRF. If only one of either QTcB or QTcF is available and it is necessary to derive the other corrected QT interval, the RR value preceding the measured QT interval should be back calculated from the collected QTc (either QTcF or QTcB) and used to compute the missing interval. If neither correction is available, do not calculate a corrected QTc value based on the collected RR, as the collected RR is the current RR interval rather than the RR interval preceeding the measured QT interval.

For reference, Fridericia's formula is:

QT interval / ((RR interval/1000)^1/3), where RR interval is in msec

For reference, Bazett's formula is:

QT interval / ((RR interval/1000)^1/2), where RR interval is in msec

9.3. Study Time Periods

9.3.1. Time in Relation to Treatment

Adverse events, serious adverse events, death, laboratory data, vitals, ECG, ECHO/MUGA, and questionnaire data (ECOG, LCSS), where appropriate, will be assigned to the study time periods defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below (see Section 9.2.4).

Pre-therapy is defined as the time prior to the subject's first dose of GSK3052230 treatment. For AE, pre-therapy will be grouped into two subcategories:

a). Pre-therapy and Pre-chemo: the time prior to the subject's first dose date of any study treatment.

b). Pre-therapy and On-chemo: the time after the first dose date of chemo treatment and prior to the first dose date of GSK3052230, for cases that the administration of chemo treatment prior to GSK3052230.

On-therapy is defined as the time from first dose of GSK3052230 treatment to the last dose date of GSK3052230 treatment plus 30 days.

Post-therapy is defined as the time after the last dose date of GSK3052230 treatment plus 30 days.

Some datasets include the first dose day as on-therapy and some exclude the first dose date as on-Therapy. The first dose day (Day 1) is considered pre-therapy for ECOG, ECG, vital signs, liver events, lab tests, and cardiac scan. The first dose day (Day 1) is considered to be on-therapy for adverse events and concomitant medications.

9.3.2. Study Time Periods for Concomitant Medications Blood and Blood Supportive Care Products

Concomitant Medication and Blood and Blood Supportive Care Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- **Start relative to treatment**: Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.
- **End relative to treatment**: Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to

'DURING' if start date falls into the on-therapy period or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the on-therapy period or (end date is missing and start relative to treatment='AFTER').

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- **Summary of Concomitant Medications**: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded. Include concomitant medication records where start relative to treatment in ('BEFORE','DURING') and end relative to treatment in ('DURING','AFTER').
- **Summary of Concomitant Medications with On-Therapy Onset**: This summary will contain medications with start date after study treatment start date. In addition, any medication that was started during post-therapy (see above for definition of post-therapy) will be excluded. Include concomitant medication records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER').

9.4. Values of Potential Clinical Importance

9.4.1. Laboratory Parameters

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

To identify laboratory values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0) will be used to assign grades to the relevant laboratory parameters. NCI-CTCAE v4.0 can be found at http://ctep.cancer.gov/reporting/ctc.html.

For laboratory data which are not listed in the NCI CTCAE v4.0, a summary of values outside the normal range will be provided.

9.4.2. ECG Parameters:

The following criteria will be used to flag electrocardiogram (ECG) values that are values of potential clinical importance:

To identify QTc (Bazett's or Fridericia's) values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign grades (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Note that there is a slight inconsistency between CTCAE v4 and ICH E14 (Absolute QTc interval prolongation). It was decided to align with CTCAE for the oncology standard categories.

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
Absolute QTcF [QTcB] interval	≥450 to <481 (Grade 1) ≥481 to <501 (Grade 2) ≥501 (Grade 3)	Msec
Increase from baseline QTcF [QTcB]	Increase of ≥31 to ≤60 Increase of >60	Msec

The following criteria will be used to flag other ECG values that are values of potential clinical importance:

ECG Parameter	Potential Clinical Importance (PCI) Range	Unit
PR interval	<110 (L) and >220 (H)	Msec
QRS interval	<75 (L) and >110 (H)	Msec

9.4.3. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline temperature	Increase to ≥38	Degrees C
Decrease from baseline Diastolic Blood Pressure	Decrease to ≤35	Degrees C

9.4.4. Left Ventricular Ejection Fraction

The following criteria will be used to flag left ventricular ejection fraction (LVEF) values that are values of potential clinical importance:

To identify LVEF values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Ejection fraction decreased'.

LVEF Parameter	Potential Clinical Importance (PCI) Range	Unit

Absolute change from baseline LVEF	• No change or any increase
	• Any decrease
	  ○ >0-<10 decrease
	  ○ 10-19 decrease
	  ○ ≥20 decrease
	  ○ ≥10 decrease and ≥ LLN
	  ○ ≥10 decrease and below LLN
	  ○ ≥20 decrease and ≥ LLN
	  ○ ≥20 decrease and below LLN
		%

Relative change from baseline LVEF	• ≥20 decrease and ≥ LLN • ≥20 decrease and below LLN	%

10. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the All Treated Subjects population, and all summaries and data listings will use treatment labels as specified in Section 7.

The list of displays for Study Population is shown in Section 20.1.1, Section 20.1.10 and Section 20.1.11 of the RAP.

10.1. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 6 will be provided. A listing of subjects excluded from analysis populations will also be provided. The population for these two displays will be the All Screened Subjects Population.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF. A listing of reasons for study withdrawal will also be provided.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who are ongoing or discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date and reason for study treatment discontinuation.

10.2. Protocol Deviations

All protocol deviations will be summarized and listed and will include inclusion/exclusion deviations as well as other deviations.

A separate summary and listing of inclusion/exclusion deviations will also be provided.

Additionally, a listing of planned and actual treatments will be provided. This will show the actual treatment given for the subject's first dose versus the planned treatment.

10.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, baseline body weight and baseline BMI) will be summarized and listed. Age, height, weight and BMI will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by <18, 18-64, 65-74, and >74. The count and percentage will be computed for sex and ethnicity.

Race and racial combinations will be summarized and listed.

Separate summaries of demographic characteristics and race and racial combinations will be provided for the Screen Failure Population.

Disease history and characteristics at initial diagnosis and screening will be listed. Separate summaries of disease characteristics at initial diagnosis and screening will be provided. Medical conditions present at screening will be listed.

A summary of disease burden at baseline will be produced. Information on sites of metastatic disease at screening will be listed.

Substance use, including smoking history and alcohol use, will be summarized and listed.

Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. The listing of prior anti-cancer therapy will show the relationship between ATC Level 1, Ingredient, and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced.

Prior anti-cancer radiotherapy will be listed. Prior cancer-related and non-cancer-related surgeries will be listed.

10.4. Concomitant Medications

Concomitant medications will be coded using GSK Drug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients. Anatomical Therapeutic Chemical (ATC) classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxicillin on two separate occasions, the subject is counted only once under the ingredient “Amoxicillin”.

In the summary of concomitant medications, the ingredients will be summarized by the base only, using CMBASECD and CMBASE.

Blood products or blood supportive care products with onset date within the on-therapy window will be included in the summary tables. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided.

11. EFFICACY

All efficacy analyses will be based on the All Treated Subjects population as defined in Section 6 unless otherwise specified. All analyses will be presented by study part and dose of study treatment. Certain analyses, identified in the text below, will be produced only for subjects who received the RP2D for each Study Part.

Efficacy assessments are based on RECIST 1.1 criteria for Parts A and B. For Part C, both RECIST 1.1 and the modified RECIST criteria for MPM subjects will be used. In other words, MPM subjects will have tumor measurements for both criteria.

For Part C, primary efficacy assessments will be based on the investigator-assessed modified RECIST criteria for MPM subjects. Note that the modified RECIST criteria affect the way the tumors are measured, however the list of variables included in datasets and format of displays are unchanged from standard RECIST criteria.

Overall Response Rate (ORR)

Overall Response Rate (ORR) is defined as the percentage of subjects achieving a confirmed CR or PR from the start of treatment until disease progression. This will be determined based on Investigator assessments of response. The best overall response data will be summarized by dose of study treatment for each study part. For Part C this display will be produced for both the RECIST and modified RECIST criteria.

Subjects with Not Evaluable (NE) or missing response will be treated as non-responders; i.e. they will be included in the denominator when calculating the percentage.

The 95% CI for response rates in each treatment arm will be calculated.

All data relating to response from the Investigator will be listed including lesion measurements, response assessments and best response. Separate listings will be provided for RECIST and Modified RECIST criteria for Part C.

A waterfall plot of the Investigator-assessed percent change from baseline in tumor measurement at time of best response will be provided for each study part, separately for RECIST and Modified RECIST Criteria for Part C. The plot will be color-coded for best overall response. Indication of the subject number and dose will be provided below the plot.

Additionally, a bar chart of duration of treatment by subject with indications for treatment arm and investigator-assessed best response by RECIST criteria will be provided for each study part. For Part C, the plot will display two investigator-assessed best responses; one for RECIST and the other for modified RECIST criteria.

For Part C, a plot of FGF2 over expression level by best overall response from modified RECIST criteria will be produced.

Volumetric Analysis: Retrospective evaluation of tumor volumes will also be performed in subjects with sufficient CT or MRI imaging data. A listing and summary of tumor volumes by response and dose will be performed.

Brain and Bone Scans

Results from brain and bone scans will be listed.

Forced vital capacity

FVC data will be listed and summarized. Additionally, change from baseline FVC will be summarized.

Tumor Growth and Tumor Kinetics Analysis

A listing of information from prior tumor scans will be provided by Clinical Statistics.

Tumor Growth and Tumor Kinetics Analysis will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Outputs will be separate from the SAC package delivered by Clinical Programming (US).

Data from some arms of the study may be combined to describe the kinetics of tumor growth based on the sum of longest diameters and/or volume of target lesions, including information from prior tumor scans if the data warrant. This analysis will be the responsibility of CPMS.

The kinetics of tumor growth may be described as a function of time using the NSCLC model described by the FDA [Wang, 2009]. The tumor size (TS) is expressed as:

$$TS(t) = BSL \bullet e^{-SRt} + PR \bullet t$$

where TS(t) denotes the tumor size measured as the sum of longest distance (mm) of lesions or volume (mm3) at time t, BSL is the baseline tumor size, SR is the exponential tumor shrinkage rate constant and PR is the linear tumor progression rate.

The kinetics of tumor growth may also be described as a function of time using the model described by Claret [Claret, 2009]. The model is expressed as:

$$dTS(t)/dt = (KL - KD \bullet e^{-\lambda t}) \bullet TS(t)$$

where TS(t) denotes the sum of longest distance (mm) of lesions or volume (mm3) at time t, with TS(0) being the baseline tumor size, KL represents the exponential tumor growth rate, KD represents the exponential rate of tumor shrinkage (i.e. drug effect on total tumor size), λ is the rate constant for drug resistance/disease progression. A measure of exposure of one or more of the administered medications may be included in the models.

The equation proposed by Wang and/or Claret will be fit to the observed data using a mixed-effects model with NONMEM VII. Other models of the kinetics of tumor growth, such as a 2-parameter model, may be used to analyze the data [Stein, 2011; Stein, 2012].

The time to tumor growth (TTG) may be estimated with parameters from the appropriate model. Subject characteristics such as baseline tumor size, performance status, LDH, age, sex, race, prior therapies, or radiotherapy, may be evaluated to determine which covariates have a significant effect on the kinetics of tumor growth.

Progression-Free Survival

An analysis of progression-free survival (PFS) will be completed using RECIST criteria for Parts A and B and Modified RECIST criteria for Part C. Only subjects who received the RP2D will be included in summary displays for PFS although PFS will be calculated and listed for all subjects. PFS is defined as the time from date of first dose of GSK3052230 to the date of first documented disease progression according to radiological or clinical assessment, or to date of death due to any cause. For subjects who do not progress or die, PFS will be censored at the time of last radiological scan. Subjects who discontinue study with no post-treatment tumor assessment will be censored at date of first dose of study drug.

A listing and summary of PFS will be produced for each study part. If there are a sufficient number of progressions or deaths, median PFS, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. A Kaplan-Meier survival curve with 90% confidence bands will also be provided for each study part.

Additionally, a shift summary comparing numerical categories of time to progression on last prior therapy to categories of progression-free survival on study may be produced if the data warrant.

Subjects who progressed or died after an extended period without adequate assessment will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the investigator determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring. As the assessment schedule may change through the course of the protocol, specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in Section 9.2.10.

Subjects should not start subsequent anti-cancer therapy while on study. However, if a subject received subsequent anti-cancer therapy while on study and prior to the date of documented events, PFS will be censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy.

If a subject has neither progressed nor died nor started new anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment defined as an assessment where the Investigator determined response is CR, PR, SD. The date of response will be used as the censoring date.

A summary of the assignments for progression and censoring dates for PFS are specified in the following table.

Table 4 Assignments for Progression and Censoring Dates for PFS Analysis

Situation	Date of Event (Progression/Death) or Censoring	Outcome Event (Progression/Death) Or Censored
No (or inadequate) baseline tumor assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Date of First Dose	Censored
No post-baseline assessments and the subject has not died (if the subject has died follow the rules for death indicted at the bottom of the table)	Date of First Dose	Censored
Progression documented between scheduled visits	Date of assessment of progression[1]	Event
No progression (or death)	Date of last 'adequate' assessment of response[2]	Censored
New anticancer treatment started (prior to documented disease progression)[3]	Date of last 'adequate' assessment of response[2] (on or prior to starting anti-cancer therapy)	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits	Date of death	Event
Death or progression after extended period without adequate assessments	Date of last 'adequate' assessment of response[2] (prior to missed assessments)	Censored

[1] The earliest of (i) Date of radiological assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiological assessment showing unequivocal progression in non target lesions, or (iii) Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions); or (iv) Date of clinical assessment of progression

[2] An adequate assessment is defined as an assessment where the Investigator determined response is CR, PR, or SD.
[3] If PD and New anti-cancer therapy occur on the same day assume the progression was documented first e.g., outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of first dose.

12. SAFETY ANALYSES

Unless otherwise specified, all the safety analyses will be based on the All Treated Subjects population as defined in Section 6 and summaries will include all events or assessments collected during the study. All the analyses will be performed by study part and treatment arm.

The list of displays for safety analyses are shown in Section 20.1.4, Section 20.1.5, Section 20.1.10 and Section 20.1.11 of the RAP.

12.1. Extent of Exposure

Extent of exposure to GSK3052230, Paclitaxel (Part A), Carboplatin (Part A), Docetaxel (Part B), Pemetrexed (Part C), and Cisplatin (Part C) will be summarized and listed separately.

For each component of study treatment, the number of cycles administered, dose intensity (dose delivered per cycle), and the cumulative dose received will be summarized with mean, median, standard deviation, minimum, and maximum. The number and percentage of subjects who received a given number of cycles (<4, 4-6, and >6 cycles) will be reported. The duration of exposure to study treatment in days (from first day to last day of treatment plus 1 day) will also be summarized.

Dose reductions will be summarised by number of reductions and reasons for reductions. Dose escalations will be summarised by number of escalations and reasons for escalation. Missed doses will be summarised by number of missed doses and reasons for missed dose. Dose delays will be summarised by number of delays, reasons for the delays, and delay duration (days). The mean, standard deviation, median, minimum value, and maximum value will be computed for the duration of delay as well as the number and percentage of the delays ≤7, 8-14, 15-21 and >21 days. If for any reasons there are dose delays flagged in CRF but not confirmed by programmatic analysis, then 'Duration of dose delays' will be set to zero and these "delays" will be excluded for the calculation of mean, median and standard deviation of the duration of dose delays.

All the dose reductions, dose escalations, missed doses and dose delays will be listed separately. Listings of incomplete infusions and infusion interruptions will also be provided.

A horizontal bar graph of duration of treatment in days (from first day to last day of treatment plus 1 day) will be produced. This graph will display duration of treatment in days for each subject along with the treatment that the subject received and the subject's best overall response.

12.2. Adverse Events

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose modifications, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

The frequency and percentage of AEs will be summarized and displayed in two ways: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.A summary of all AEs will be provided by SOC with SOC's displayed in descending order of total incidence by SOC and with AEs within each SOC in descending order of total incidence within the SOC.

The relationship between MedDRA SOC, PT, and Verbatim Text will be listed.

Adverse events (AEs) will be graded according to the CTCAE, Version 4.0. Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary).

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by Preferred term (PT) in descending order of total incidence. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

Separate summaries will be provided for study treatment-related AEs in the same two ways as for overall AEs: 1) in descending order of total incidence by PT only and 2) in descending order of total incidence by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

All AEs will be listed, including grade change details. For treatment-related AEs, the treatment to which the AE was related will be shown. Additionally, a listing of subject IDs for each individual AE will be produced.

A listing of adverse events recorded as dose-limiting toxicities will be provided. Additionally, a summary of the number of patients experiencing DLT's in each cohort will be provided. A listing showing what DLT's were recorded by cohort will also be provided.

12.3. Adverse Events of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

The events of special interest included from protocol Section 1.6 (Summary of Risk Management). This section includes the following events:

- Infusion-related reactions/Edema/Hypersensitivity
- Anti-drug antibodies (would not be associated with specific AEs)
- Anterior uveitis
- Wound healing
- Bowel perforation
- Heart valve fibrosis
- Peripheral Neuropathy
- Hypothyroidism
- Hematologic toxicity
- Nephrotoxicity
- Ototoxicity

Summaries of the number and percentage of subjects with these events will be provided for each type of events separately. The summary of event characteristics will also be provided, including number of subjects with any event, number of events, number of subjects with any event that is serious, number of subjects with any event that is related to study treatment, the outcome of the event, maximum grade and the action taken for the event. The percentage will be calculated with the denominator as total number of subjects. The worst case approach will be applied at subject level for the event outcome and maximum grade, i.e. a subject will only be counted once as the worst case from all the events experienced by the subject. For action taken to an event, subject will be counted once under each action, e.g. if a subject has an event leading to both study treatment discontinuation and dose reduction, the subject will be counted once under both actions.

In addition, AEs of special interest will be listed separately.

Depending on the event, some additional analysis may be implemented (example: infusion and duration on study or response).

12.4. Deaths and Serious Adverse Events

In the event that a subject has withdrawn consent, no data after the withdrawal of consent date from this subject including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths will be summarized based on the number and percentage of subjects. This summary will classify subjects by primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs, fatal SAEs and study treatment-related fatal SAEs. The summary tables will be displayed in descending order of total incidence by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs.

12.5. Adverse Events Leading to Discontinuation of Study Treatment and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of total incidence by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Discontinuation of Study Treatment
- AEs Leading to Dose Delays
- AEs Leadings to Dose Reductions

12.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If a subject or subject's partner becomes pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

12.7. Clinical Laboratory Evaluations

The assessment of laboratory toxicities will examine the following laboratory tests as specified in Table 5:

Table 5 List of Clinical Laboratory Tests

Hematology	
Platelet Count	*Automated WBC Differential:*
Red blood cell (RBC) Count	Neutrophils (absolute)
White blood cell (WBC) Count (absolute)	Lymphocytes (absolute)
Hemoglobin	Monocytes (absolute)
	Eosinophils (absolute)
	Basophils (absolute)
Clinical Chemistry	
Potassium, Sodium, Chloride, Total carbon dioxide, total Calcium, ionized calcium, magnesium, phosphate, albumin, glucose (fasting),	
Blood urea nitrogen (BUN), Creatinine, Uric Acid, creatinine clearance	
Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma glutamyl transferase (GGT), Alkaline phosphatase, Total bilirubin (if elevated also test direct bilirubin)	
Thyroid hormone: TSH at Screening; every 2 cycles for the first year and then every 4 cycles. If TSH is positive, also test total T3, total T4, and free T4.	
Pancreatic tests (amylase and lipase)	
Coagulation tests (prothrombin time, partial thromboplastin time, international normalized ratio, and fibrinogen)	
Routine Urinalysis	
pH, glucose, protein, blood and ketones by dipstick	
Microscopic examination (if blood or protein is abnormal)	
Other screening tests	
Pregnancy test for females (serum at screening, urine or serum post dose)	

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v4.0). However, some tests are not graded using CTCAE.

For hematology, RBC is not gradable by CTCAE v4.0.

For clinical chemistry**,** BUN and creatinine clearance are not gradable by CTCAE v4.0. For sodium, potassium, calcium, glucose, and magnesium there will be two bi-directional parameters (hyper and hypo) created and the tests will be graded by CTCAE v4.0 in both directions.

For coagulation tests, INR and partial thromboplastin time are gradable by CTCAE v4.0 but prothrombin time is not.

For thyroid function tests, neither the thyroid-stimulating hormone (TSH) test nor the free thyroxine (T4) test is gradable by CTCAE v4.0.

Separate summary tables for hematology and chemical chemistry will be produced as detailed below. Liver function, coagulation, thyroid and pancreatic laboratory tests will be included with chemical chemistry.

Summaries of lab data by maximum toxicity grade will be provided.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. These summaries will display the number and percentage of subjects with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.0, summaries of worst case changes from baseline with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst case post-baseline. If a subject has a decrease to low and an increase to high during the post-baseline period, then the subject is counted in both the "Decrease to Low" categories and the "Increase to High" categories.

A supporting listing of all laboratory data will be provided.

Detailed derivation of baseline assessment is specified in Section 9.2.5.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

Dipstick test results from urinalysis will be summarized at each scheduled visit. A supporting listing with subject level details will be provided.

12.7.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided in addition to what has been described above.

Possible Hy's law cases are defined as any elevated (ALT≥3×ULN **and** total bilirubin≥2×ULN (with direct bilirubin ≥35% of total bilirubin, if direct bilirubin is measured)) **OR** (ALT ≥3×ULN **and** INR >1.5, if INR is measured). Note that INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants.

LFT patient profiles plots for subjects experiencing an ALT, AST or total bilirubin of toxicity grade 2 or above will be produced.

A plot of maximum total bilirubin versus maximum ALT will be generated. A trellis display of LFT shifts from baseline to maximum values will be provided. A matrix display of LFT results will also be produced.

12.8. Other Safety Measures

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

Vital Signs

Vital sign data will be listed. Values of vital signs as well as the change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

In addition vital signs values will be categorized as follows:

- Systolic BP (mmHg): Grade 0 (<120), Grade 1 (≥120-<140), Grade 2 (≥140-<160) and Grade 3 (≥160)
- Diastolic BP (mmHg): Grade 0 (<80), Grade 1 (≥80-<90), Grade 2 (≥90-<100), and Grade 3 (≥100)
- Heart rate (beats/min): <60, 60-100, and >100
- Temperature (°C): <35, 35-38, ≥38

Summaries of increase in vital signs from the baseline with respect to the categories defined above will be performed. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled assessment time and in the worst case post-baseline.

Performance Status

ECOG performance status will be summarized at baseline and each post-baseline scheduled visit. Summaries will use frequency and percentage of subjects at each planned assessment time. A summary of change from baseline by scheduled visits will be performed, as well as the worst case post-baseline and the best case post-baseline changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings will be displayed by scheduled visits as well as for the worst case post-baseline.

The QTc values based on Fridericia's formula will be rounded to the integer and the values will be categorized into the following ranges: Grade 0 (<450), Grade 1 (450-480),

Grade 2 (481-500), and Grade 3 (≥501). Summaries of grade increase will be provided. These summaries will display the number and percentage of subjects with any grade increase, increase to grade 2 and increase to grade 3 at each scheduled assessment time and in the worst case post-baseline.

The changes in QTc values will be categorized into the clinical concern ranges which are specific to changes in QTc: 31-60 and >60 msec. A summary of change in QTc value will display the number and percentage of subjects with a change within each range at each scheduled assessment time and in the worst case post-baseline. Subjects with missing baseline values will be excluded from this summary.

The summaries for the QTc will use the collected value based on Fridericia's formula.

In addition, ECG interval values will be also be summarized.

Listings of abnormal ECG findings and a listing of ECG values will be provided.

A figure plotting the baseline QTc and the worst-case post-baseline values will be produced. The figure will have reference lines at 480 and 500 msec for both the ordinate and the abscissa axes. There will be diagonal reference lines at equality (i.e. a 45 degree line), at equality plus 30 msec, and at equality plus 60 msec.

LVEF (ECHO)

Absolute change from baseline in LVEF will be summarized at each scheduled assessment time and in the worst case post-baseline. Only the post-baseline assessments that used the same method (ECHO or MUGA) as the baseline assessments will be used to derive the change from baseline. The change from baseline will be categorized as follows:

- Any increase
- No change
- Any decrease:
  - 0 - <10% Decrease
  - 10 - <20% Decrease
  - ≥20% Decrease
- ≥10% decrease and ≥ LLN
- ≥10% decrease and < LLN
- ≥20% decrease and ≥ LLN
- ≥20% decrease and < LLN

LVEF results will also be listed with subject level details including absolute change from baseline.

Liver Events

For any liver events that occur during the study, the liver event information for RUCUM score will be summarized, including whether the subject was age 55 or over, whether the subject became pregnant, liver imaging normal or not, a biopsy was taken or not, whether there was fasting or significant dietary change, whether the subject took any unconventional medications, timing when the event occurs (while on treatment or after stopping treatment) and summary statistics for time from first dose to start of liver event and time from last dose to start of liver event. If the number of events does not support a summary, then only listings will be produced.

For subjects with multiple events, the first event will be used for the summary tables. All events with subject level details will be displayed in a supporting listing.

Ocular Exams

Baseline ocular history and risk factors for cataracts will be summarized and listed.

Summaries showing the number and percentage of normal and abnormal findings by scheduled visit and eye location (right or left) will be produced for external eye exam findings, indirect fundoscopic findings, and findings from the slit lamp exam excluding lens. Abnormal findings will be listed separately for each type of exam.

A categorical summary of the slit lamp examination using AREDS clinical lens opacity grading will be produced by scheduled visit and eye location.

A summary of intraocular pressure and change from baseline intraocular pressure as measured by tonometry will be produced by scheduled visit and eye location.

A categorical summary of corrected visual acuity and a shift summary of corrected visual acuity will be produced by scheduled visit and eye location.

All eye exam data will be listed, with separate listings for each type of eye examination.

Visual AEs will be summarized as describe in Section 12.2.

Immunogenicity

A listing of anti-GSK3052230 immunogenicity results will be produced. If any samples contain anti-GSK3052230 antibodies as determined by the ECL screening assay, they will be further characterized for specificity and antibody titers and these results will be included in the listing.

A summary of anti-GSK3052230 immunogenicity results will show the number and percent of subjects with samples containing anti-GSK3052230 antibodies.

13. HEALTH OUTCOMES ANALYSES

The Lung Cancer Symptom Scale (LCSS) for patients with lung cancer or LCSS-meso for MPM patients is self-administered by subjects (patient scales) and completed by the

investigator (observer scales) at screening, on day 1 of every cycle, and at the post-study visit. The LCSS consists of 9 patient-reported components and 6 observer-reported components. Using visual analogue scales (range from 0 to100), the patient scale measures the intensity of patient responses for appetite, fatigue, cough, hemoptysis, dyspnea, pain, and summary items overall symptomatic distress, interference with normal activities, and global quality of life. The observer items are scored categorically as None (100), Mild (75), Moderate (50), Marked (25), and Severe (0). The observer items are loss of appetite, fatigue, cough, hemoptysis, dyspnea, and pain. The LCSS-meso questionnaire has 8 patient-reported components and 5 observer-reported components as hemoptysis is not included.

All collected data for LCSS (Parts A and B) and LCSS-Meso (Part C) will be listed.

A summary of LCSS (or LCSS-Meso) patient component scores and a summary of observer-assessed component scores will be provided. These summaries will be provided by scheduled visit. In addition, a summary of LCSS (or LCSS-Meso) change from baseline patient scores for patient component scores will be provided. The change from baseline summary will be produced by visit and will also include a "best case post-baseline" row. Shift summaries for observer-assessed scores will be produced for each component by scheduled visit and will include a best case post-baseline row.

A summary of the number of patients with improvement in ≥2 observer-assessed scores at any one time point will be produced. Similarly, a categorical summary of the number and percentage of patients achieving at least a 10mm improvement in at least one patient-assessed component at any time point will be provided.

Spaghetti plots of patient-assessed components will be provided for each component, with data from observers overlaid. Median plots over time will also be provided for each component for both patient-assessed and observer components.

If the data warrant, the relationship between best overall response by RECIST (modified RECIST for MPM) and LCSS (LCSS-Meso for MPM) assessments may be explored. Plots of patient-assessed component best change from baseline by category of best overall response may be produced for components of particular interest. In addition, a contingency table showing the number and percentage of patients achieving improvement in ≥2 observer-assessed scores at any one time point by category of best overall response may be provided.

If the data warrant, comparisons of patient-assessed and observer-assessed components may be made. Graphs of best case change from baseline in patient-assessed scores by best case change from baseline in observer-assessed scores may be created for components of particular interest.

If warranted, mixed-effects models may be used to model subject data over time for patient-assessed components of particular interest. Independent variables may include the baseline component score and time as fixed effects and subject as a random effect.

14. PHARMACOKINETIC ANALYSES

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Data Sciences - Oncology, GlaxoSmithKline.

The merge of PK concentration data and CRF data to generate a dataset with actual blood sampling times, actual time relative to dosing, and PK concentrations as well as the listings and summaries of concentration data will be performed after DBF by, or under the direct auspices of, Clinical Programming (US), GlaxoSmithKline.

Population PK analyses will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK.

Derivation of pharmacokinetic parameters for subjects with extensive PK sampling only, will be performed by, or under the direct auspices of, Clinical Pharmacology Modeling and Simulation (CPMS), GlaxoSmithKline.

Statistical analysis of the pharmacokinetic parameters for subjects undergoing extensive PK sampling will be performed by, or under the direct auspices of, Clinical Statistics (US), GlaxoSmithKline.

Unless otherwise stated, all tables, figures and listings in this section will be based on the Pharmacokinetic Population, and all summaries, figures and data listings will use treatment labels specified in Section 7.1.

The list of displays for PK is shown in Section 20.1.6, Section 20.1.7 and Section 20.1.10 of the RAP.

14.1. Drug Concentration Measures

Concentrations of GSK3052230, Paclitaxel, Docetaxel, and Pemetrexed in plasma will be listed and summarized by study part, treatment group and nominal time. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance document GUI_51487, “Non-Compartmental Analysis of Pharmacokinetic Data”, for more information regarding the handling of plasma concentrations below the assay’s lower limit of quantification (NQ). For the subset of subjects who undergo extensive PK sampling for GSK3052230, individual, mean, and median concentration plots will be produced for the extensive sampling days, with the profile for Cycle 1 Day 1 through the pre-infusion concentration for Cycle 2 Day 1 included (i.e., x-axis ends at Cycle 2 Day 1 timepoint). Separate individual, mean, and median concentration plots will focus on Cycle 1 Day 1 through the first 24-hour period only. For the subset of subjects who undergo extensive PK sampling for Paclitaxel, Docetaxel, and Pemetrexed, individual, mean, and median concentration plots will be produced for the extensive sampling day, with the profile for Cycle 2 Day 1 (i.e., x-axis ends at Cycle 2 Day 1 12 hours).

Box and whisker plots showing pre-infusion concentration data vs. Study Arm will be separately provided for Cycle 1 Day 8, Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1 and

Cycle 12 Day 1. Similar plots will be created for the concentrations at the end of GSK3052230 infusion on those days.

14.2. Deriving and Summarizing Pharmacokinetic Parameters

For subjects in Arms A, B, and C who undergo extensive PK sampling, the following pharmacokinetic parameters will be determined from the plasma concentration-time data for GSK3052230. The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin Professional, version 3.0 or higher. All calculations of non-compartmental parameters will be based on actual sampling times.

1. The first occurrence of the maximum observed plasma concentration determined directly from the raw concentration-time data (Cmax).
2. The time at which Cmax is observed will be determined directly from the raw concentration-time data (tmax).

PK parameters of GSK3052230 will be listed and summarized separately for Arms A, B, and C, and by dose for subjects in the extensive PK sampling group only. All derived PK parameters will be listed. For Cmax the following summary statistics will be calculated for each study part, dose, and study day for which PK parameters were calculated: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. For tmax, median, maximum, minimum, arithmetic mean, 95% confidence interval, and standard deviation will be calculated. All PK parameters will be reported to at least 3 significant digits, but to no more significant digits than the precision of the original data.

14.3. Population Pharmacokinetic Analyses

Population PK analysis will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Plasma GSK3052230 concentration-time from patients with extensive and limited sampling may be combined with data from other studies and will be analyzed using a population pharmacokinetic approach. A nonlinear mixed effects model will be used to determine population pharmacokinetic parameters (clearances, CL and volumes of distribution, V) and identify important covariates (e.g., age, weight, or disease related covariates). Summary exposure measures (Cmax, AUC and average concentration Cav defined as time corrected AUC [AUC/τ]) will also be computed. Results of this analysis may be provided in a separate report.

15. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

PK/PD analyses will be the responsibility of Clinical Pharmacokinetics/Modelling & Simulation, GSK. Outputs generated from this analysis will be separate from outputs produced by Clinical Programming (US). Observed or predicted concentrations or summary exposure measure (eg; Cmax, Ctrough, and Cav) may be combined with safety

and efficacy pharmacodynamic measures of interest to examine potential exposure response relationships. Graphical evaluation will first be performed.

Where evidence of activity is seen, linear and/or non-linear mixed effect models may be fitted to the data to estimate PK/PD parameters of interest (e.g. slope, baseline (E0), concentration for 50% of maximum effect (EC50) and maximum effect (Emax)).

If needed for analysis, a PK/PD analysis data set will be generated by Clinical Programming (US).

16. IMMUNOGENECITY ANALYSES

For the immunogenicity assessment, serum will be tested for the presence of anti-GSK3052230 antibodies using one type of antibody assays, i.e. a binding assay. For the binding assay, there will be 3-steps testing schema: screening, confirmation and titration steps. A screening assessment is performed which produces a result of positive or negative. For samples with a positive screening result, a confirmatory assay is then carried out, which also produces a result of positive or negative. For samples with a positive confirmation result, a titer value will also be obtained to quantify the degree of binding in the titration assay step. Patients will be viewed as positive for the binding assay if the confirmatory assay was positive.

For the incidence of patients with positive binding antibody, a table will be produced summarizing results for the binding antibody assay by treatment group and visit. The table will include the number and proportion of subjects in each result category for each visit (including early withdrawal visit). Binding confirmatory assay results will be categorized as negative, transient positive (defined as a single positive immunogenic response that does not occur at the final assessment) or persistent positive (defined as a positive immunogenic response at least 2 consecutive assessments or a single result at the final assessment). A separate table will be produced summarizing the confirmatory assay results by treatment group and visit.

For the titer value, a table will be produced to summarize the median, min and max titer values among all visits by treatment group. This table will also summarize the median, min and max of the highest titer values from each subject.

17. TRANSLATIONAL RESEARCH

17.1. FGF Biomarkers Analyses

In Arms A and B, a requirement for inclusion is evidence of *FGFR1* gene amplification in tumor tissue as determined by a central laboratory (CLIA or appropriate certification) using a laboratory developed test.

In Arm C, FGF2 expression will be evaluated retrospectively by IHC to determine if expression levels of FGF2 are associated with response to GSK3052230.

Any remaining tissue from this study may be used for:

- Development and validation of a potential IUO assay and companion diagnostic test, e.g., *FGFR1* gene amplification by FISH or FGF2 expression by IHC.
- Alternative biomarkers of FGF pathway signalling.
- Biomarker research (protein, RNA and DNA) including status of RTK/PI3K/AKT pathways and cancer development and additional testing of DNA, RNA, or protein biomarkers related to the function of GSK3052230 if ongoing research identifies or defines additional predictive and prognostic biomarkers

Exploratory analysis may be performed to examine potential relationships between anticancer activity and changes in markers of deregulation of FGF signaling pathway (example: *FGFR1* gene amplification) or tumor biology (e.g. cytokines, acute phase proteins, relevant transcripts and/or proteins) or between anticancer activity and potential markers of sensitivity.

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

17.1.1. FGFR1 Gene Amplification Assay

For Arm A and B, a fluorescence *in situ* hybridization (FISH) -based FGFR1 assay will be performed for the detection of abnormalities in tissue samples. FGFR1 assay will be performed one time on tissue samples from each subject. For each of Arm A, Arm B and Arm A+B, two summary tables will be produced to summarize the FGFR1 assay results.

- A table to summarize n, mean, median, standard deviation, minimum and maximum of the following FGFR1 quantitative results of all treated subjects across all treatment dose levels.
  - FGFR1/CEP Ratio
  - Average FGFR1 Signals per Cell
  - Average CEP 8 signals per Cell
  - Percentage of tumor nuclei containing ≥5 FGFR1 signals
- A table to summarize frequency of amplified samples, amplification rates (in percentage) out of interpretable samples, and overall amplification rates (in percentage) out of all samples including interpretable and non-interpretable samples.

Scatterplots will be produced to show the correlation among the following FGFR1 quantitative results which used for establishing gene amplification criteria.

- FGFR1/CEP Ratio vs. Average FGFR1 Signals per Cell
- FGFR1/CEP Ratio vs. Percentage of tumor nuclei containing ≥5 FGFR1 signals
- Average FGFR1 Signals per Cell vs. Percentage of tumor nuclei containing ≥5 FGFR1 signals

In addition, plots of FGFR1 quantitative results by best response (in terms of RECIST 1.1 criteria), FGFR1 quantitative results vs. duration of treatment, and FGFR1 quantitative results vs. PFS will be produced.

17.1.2. FGF2 Immunohistochemistry Assay

For Arm C, the FGF2 immunohistochemistry assay will be performed to specifically detect the expression of the FGF2 in human mesothelium tissue. For each subject enrolled in Arm C, the FGF2 assay will be performed once on tissue samples. Nuclear staining and cytoplasm staining are to be scored using qualitative scoring criteria (0= no staining, 1+ = weak staining, 2+ = moderate staining, 3+ = strong staining), along with an estimation of the percentage of cell type demonstrating that staining pattern. The H-score is then determined based on the staining scores using the following formula:

H-score = (Percentage of no staining × 0) + (Percentage of weak staining × 1)
+ (Percentage of moderate staining × 2) + (Percentage of strong scoring × 3)

A listing to display the H-score of cytoplasma staining, H-score of nuclear staining, best responses (in terms of RECIST 1.1 criteria), duration of treatment and PFS for each subject will be produced.

Plots of H-scores by best response, H-score vs. duration of treatment, and H-score vs. PFS will be produced.

18. PHARMACOGENETICS

A listing of sample accountability will be provided, showing which subjects gave samples for PGx analysis. PGx analysis, if done, will be the subject of a separate PGx RAP.

19. REFERENCES

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20. APPENDICES

20.1. Appendix 1: Data Displays

20.1.1. Study Population Tables

Table No.	Title	Population
1.0010	Summary of Study Populations, Arm A	All Screened Subjects
1.0020	Summary of Study Populations, Arm B	All Screened Subjects
1.0030	Summary of Study Populations, Arm C	All Screened Subjects
1.1110	Summary of Subject Disposition, Arm A	All Treated Subjects
1.1120	Summary of Subject Disposition, Arm B	All Treated Subjects
1.1130	Summary of Subject Disposition, Arm C	All Treated Subjects
1.1210	Summary of Study Treatment Status, Arm A	All Treated Subjects
1.1220	Summary of Study Treatment Status, Arm B	All Treated Subjects
1.1230	Summary of Study Treatment Status, Arm C	All Treated Subjects
1.1310	Summary of Inclusion/Exclusion Criteria Deviations, Arm A	All Treated Subjects
1.1320	Summary of Inclusion/Exclusion Criteria Deviations, Arm B	All Treated Subjects
1.1330	Summary of Inclusion/Exclusion Criteria Deviations, Arm C	All Treated Subjects
1.1410	Summary of Protocol Deviations, Arm A	All Treated Subjects
1.1420	Summary of Protocol Deviations, Arm B	All Treated Subjects
1.1430	Summary of Protocol Deviations, Arm C	All Treated Subjects
1.2010	Summary of Demographic Characteristics, Arm A	All Treated Subjects
1.2020	Summary of Demographic Characteristics, Arm B	All Treated Subjects
1.2030	Summary of Demographic Characteristics, Arm C	All Treated Subjects
1.2040	Summary of Demographic Characteristics for Screen Failure Population, Arm A	Assay Validation
1.2050	Summary of Demographic Characteristics for Screen Failure Population, Arm B	Assay Validation
1.2060	Summary of Race and Racial Combination Details, Arm A	All Treated Subjects
1.2070	Summary of Race and Racial Combination Details, Arm B	All Treated Subjects
1.2080	Summary of Race and Racial Combination Details, Arm C	All Treated Subjects
1.2090	Summary of Race and Racial Combination Details for Screen Failure Population, Arm A	Assay Validation
1.2091	Summary of Race and Racial Combination Details for Screen Failure Population, Arm B	Assay Validation
1.2110	Summary of Disease Burden at Baseline, Arm A	All Treated Subjects
1.2120	Summary of Disease Burden at Baseline, Arm B	All Treated Subjects
1.2130	Summary of Disease Burden at Baseline, Arm C	All Treated Subjects
1.2140	Summary of Substance Use, Arm A	All Treated Subjects
1.2150	Summary of Substance Use, Arm B	All Treated Subjects
1.2160	Summary of Substance Use, Arm C	All Treated Subjects
1.3210	Summary of Disease Characteristics at Initial Diagnosis, Arm A	All Treated Subjects
1.3220	Summary of Disease Characteristics at Initial Diagnosis, Arm B	All Treated Subjects

Table No.	Title	Population
1.3230	Summary of Disease Characteristics at Initial Diagnosis, Arm C	All Treated Subjects
1.3240	Summary of Disease Characteristics at Screening, Arm A	All Treated Subjects
1.3250	Summary of Disease Characteristics at Screening, Arm B	All Treated Subjects
1.3260	Summary of Disease Characteristics at Screening, Arm C	All Treated Subjects
1.4010	Summary of Prior Anti-Cancer Therapy, Arm B	All Treated Subjects
1.4020	Summary of Prior Anti-Cancer Therapy, Arm C	All Treated Subjects
1.4030	Summary of Prior Dictionary Coded Anti-Cancer Therapy, Arm B	All Treated Subjects
1.4040	Summary of Prior Dictionary Coded Anti-Cancer Therapy, Arm C	All Treated Subjects
1.4050	Summary of Number of Prior Anti-Cancer Therapy Regimens, Arm B	All Treated Subjects
1.4060	Summary of Number of Prior Anti-Cancer Therapy Regimens, Arm C	All Treated Subjects
1.4070	Summary of Best Response to Most Recent Prior Anti-Cancer Therapy, Arm B	All Treated Subjects
1.4080	Summary of Best Response to Most Recent Prior Anti-Cancer Therapy, Arm C	All Treated Subjects
1.5010	Summary of Concomitant Medications by Ingredient, Arm A	All Treated Subjects
1.5020	Summary of Concomitant Medications by Ingredient, Arm B	All Treated Subjects
1.5030	Summary of Concomitant Medications by Ingredient, Arm C	All Treated Subjects
1.5040	Summary of Blood Products after Start of Study Medication, Arm A	All Treated Subjects
1.5050	Summary of Blood Products after Start of Study Medication, Arm B	All Treated Subjects
1.5060	Summary of Blood Products after Start of Study Medication, Arm C	All Treated Subjects
1.5070	Summary of Blood Supportive Care Products after the Start of Study Medication, Arm A	All Treated Subjects
1.5080	Summary of Blood Supportive Care Products after the Start of Study Medication, Arm B	All Treated Subjects
1.5090	Summary of Blood Supportive Care Products after the Start of Study Medication, Arm C	All Treated Subjects

20.1.2. Efficacy Tables

No.	Title	Population
2.0010	Summary of Investigator-Assessed Best Response with Confirmation (RECIST 1.1 Criteria), Arm A	All Treated Subjects
2.0020	Summary of Investigator-Assessed Best Response with Confirmation (RECIST 1.1 Criteria), Arm B	All Treated Subjects
2.0030	Summary of Investigator-Assessed Best Response with Confirmation (RECIST 1.1 Criteria), Arm C	All Treated Subjects
2.0040	Summary of Investigator-Assessed Best Response without Confirmation (RECIST 1.1 Criteria), Arm A	All Treated Subjects
2.0050	Summary of Investigator-Assessed Best Response without Confirmation (RECIST 1.1 Criteria), Arm B	All Treated Subjects

No.	Title	Population
2.0060	Summary of Investigator-Assessed Best Response without Confirmation (RECIST 1.1 Criteria), Arm C	All Treated Subjects
2.0070	Summary of Investigator-Assessed Best Response with Confirmation (Modified RECIST Criteria), Arm C	All Treated Subjects
2.0080	Summary of Investigator-Assessed Best Response without Confirmation (Modified RECIST Criteria), Arm C	All Treated Subjects
2.1010	Summary of Kaplan-Meier Estimates of Investigator-Assessed Progression-Free Survival, Arm A	All Treated Subjects
2.1020	Summary of Kaplan-Meier Estimates of Investigator-Assessed Progression-Free Survival, Arm B	All Treated Subjects
2.1030	Summary of Kaplan-Meier Estimates of Investigator-Assessed Progression-Free Survival, Arm C	All Treated Subjects

20.1.3. Efficacy Figures

No.	Title	Population
12.0010	Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Tumor Measurement (RECIST 1.1 Criteria), Arm A	All Treated Subjects
12.0020	Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Tumor Measurement (RECIST 1.1 Criteria), Arm B	All Treated Subjects
12.0030	Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Tumor Measurement (RECIST 1.1 Criteria), Arm C	All Treated Subjects
12.0040	Investigator-Assessed Percent Change at Maximum Reduction from Baseline in Tumor Measurement (Modified RECIST Criteria), Arm C	All Treated Subjects
12.0050	Graph of Kaplan Meier Investigator-Assessed Progression-Free Survival Curve with 95% Confidence Band at the Recommended Phase 2 Dose, Arm A	All Treated Subjects
12.0060	Graph of Kaplan Meier Investigator-Assessed Progression-Free Survival Curve with 95% Confidence Band at the Recommended Phase 2 Dose, Arm B	All Treated Subjects
12.0070	Graph of Kaplan Meier Investigator-Assessed Progression-Free Survival Curve with 95% Confidence Band at the Recommended Phase 2 Dose, Arm C	All Treated Subjects

20.1.4. Safety Tables

No.	Title	Population
3.0010	Summary of Exposure to GSK3052230, Arm A	All Treated Subjects
3.0020	Summary of Exposure to GSK3052230, Arm B	All Treated Subjects
3.0030	Summary of Exposure to GSK3052230, Arm C	All Treated Subjects
3.0040	Summary of Exposure to Paclitaxel, Arm A	All Treated Subjects
3.0050	Summary of Exposure to Carboplatin, Arm A	All Treated Subjects
3.0060	Summary of Exposure to Docetaxel, Arm B	All Treated Subjects

No.	Title	Population
3.0070	Summary of Exposure to Pemetrexed, Arm C	All Treated Subjects
3.0080	Summary of Exposure to Cisplatin, Arm C	All Treated Subjects
3.0090	Summary of Dose Reductions of GSK3052230, Arm A	All Treated Subjects
3.0100	Summary of Dose Reductions of GSK3052230, Arm B	All Treated Subjects
3.0110	Summary of Dose Reductions of GSK3052230, Arm C	All Treated Subjects
3.0120	Summary of Dose Reductions of Paclitaxel, Arm A	All Treated Subjects
3.0130	Summary of Dose Reductions of Carboplatin, Arm A	All Treated Subjects
3.0140	Summary of Dose Reductions of Docetaxel, Arm B	All Treated Subjects
3.0150	Summary of Dose Reductions of Pemetrexed, Arm C	All Treated Subjects
3.0160	Summary of Dose Reductions of Cisplatin, Arm C	All Treated Subjects
3.0170	Summary of Dose Delays of GSK3052230, Arm A	All Treated Subjects
3.0180	Summary of Dose Delays of GSK3052230, Arm B	All Treated Subjects
3.0190	Summary of Dose Delays of GSK3052230, Arm C	All Treated Subjects
3.0200	Summary of Dose Delays of Paclitaxel, Arm A	All Treated Subjects
3.0210	Summary of Dose Delays of Carboplatin, Arm A	All Treated Subjects
3.0220	Summary of Dose Delays of Docetaxel, Arm B	All Treated Subjects
3.0230	Summary of Dose Delays of Pemetrexed, Arm C	All Treated Subjects
3.0240	Summary of Dose Delays of Cisplatin, Arm C	All Treated Subjects
3.0250	Summary of Missed Doses of GSK3052230, Arm A	All Treated Subjects
3.0260	Summary of Missed Doses of GSK3052230, Arm B	All Treated Subjects
3.0270	Summary of Missed Doses of GSK3052230, Arm C	All Treated Subjects
3.0280	Summary of Missed Doses of Paclitaxel, Arm A	All Treated Subjects
3.0290	Summary of Missed Doses of Carboplatin, Arm A	All Treated Subjects
3.0300	Summary of Missed Doses of Docetaxel, Arm B	All Treated Subjects
3.0310	Summary of Missed Doses of Pemetrexed, Arm C	All Treated Subjects
3.0320	Summary of Missed Doses of Cisplatin, Arm C	All Treated Subjects
3.0330	Summary of Dose Escalations of GSK3052230, Arm A	All Treated Subjects
3.0340	Summary of Dose Escalations of GSK3052230, Arm B	All Treated Subjects
3.0350	Summary of Dose Escalations of GSK3052230, Arm C	All Treated Subjects
3.0360	Summary of Dose Escalations of Paclitaxel, Arm A	All Treated Subjects
3.0370	Summary of Dose Escalations of Carboplatin, Arm A	All Treated Subjects
3.0380	Summary of Dose Escalations of Docetaxel, Arm B	All Treated Subjects
3.0390	Summary of Dose Escalations of Pemetrexed, Arm C	All Treated Subjects
3.0400	Summary of Dose Escalations of Cisplatin, Arm C	All Treated Subjects
3.1010	Adverse Event Overview, Arm A	All Treated Subjects
3.1020	Adverse Event Overview, Arm B	All Treated Subjects
3.1030	Adverse Event Overview, Arm C	All Treated Subjects
3.1040	Summary of All Adverse Events by System Organ Class, Arm A	All Treated Subjects
3.1050	Summary of All Adverse Events by System Organ Class, Arm B	All Treated Subjects
3.1060	Summary of All Adverse Events by System Organ Class, Arm C	All Treated Subjects
3.1070	Summary of All Adverse Events by Preferred Term, Arm A	All Treated Subjects

No.	Title	Population
3.1080	Summary of All Adverse Events by Preferred Term, Arm B	All Treated Subjects
3.1090	Summary of All Adverse Events by Preferred Term, Arm C	All Treated Subjects
3.1091	Summary of Adverse Events By Maximum Toxicity Grade, Arm A	All Treated Subjects
3.1092	Summary of Adverse Events By Maximum Toxicity Grade, Arm B	All Treated Subjects
3.1093	Summary of Adverse Events By Maximum Toxicity Grade, Arm C	All Treated Subjects
3.1094	Summary of Dose-Limiting Toxicities during the Determinative Period, Arm A	All Treated Subjects
3.1095	Summary of Dose-Limiting Toxicities during the Determinative Period, Arm B	All Treated Subjects
3.1096	Summary of Dose-Limiting Toxicities during the Determinative Period, Arm C	All Treated Subjects
3.1110	Summary of Adverse Events Related to Study Treatment by System Organ Class, Arm A	All Treated Subjects
3.1120	Summary of Adverse Events Related to Study Treatment by System Organ Class, Arm B	All Treated Subjects
3.1130	Summary of Adverse Events Related to Study Treatment by System Organ Class, Arm C	All Treated Subjects
3.1140	Summary of Adverse Events Related to Study Treatment by Preferred Term, Arm A	All Treated Subjects
3.1150	Summary of Adverse Events Related to Study Treatment by Preferred Term, Arm B	All Treated Subjects
3.1160	Summary of Adverse Events Related to Study Treatment by Preferred Term, Arm C	All Treated Subjects
3.1210	Summary of Serious Adverse Events, Arm A	All Treated Subjects
3.1220	Summary of Serious Adverse Events, Arm B	All Treated Subjects
3.1230	Summary of Serious Adverse Events, Arm C	All Treated Subjects
3.1310	Summary of Serious Adverse Events Related to Study Treatment, Arm A	All Treated Subjects
3.1320	Summary of Serious Adverse Events Related to Study Treatment, Arm B	All Treated Subjects
3.1330	Summary of Serious Adverse Events Related to Study Treatment, Arm C	All Treated Subjects
3.1410	Summary of Fatal Adverse Events, Arm A	All Treated Subjects
3.1420	Summary of Fatal Adverse Events, Arm B	All Treated Subjects
3.1430	Summary of Fatal Adverse Events, Arm C	All Treated Subjects
3.1440	Summary of Fatal Adverse Events Related to Study Treatment, Arm A	All Treated Subjects
3.1450	Summary of Fatal Adverse Events Related to Study Treatment, Arm B	All Treated Subjects
3.1460	Summary of Fatal Adverse Events Related to Study Treatment, Arm C	All Treated Subjects
3.1510	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Arm A	All Treated Subjects
3.1520	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Arm B	All Treated Subjects

No.	Title	Population
3.1530	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Arm C	All Treated Subjects
3.1540	Summary of Adverse Events Leading to Dose Reductions, Arm A	All Treated Subjects
3.1550	Summary of Adverse Events Leading to Dose Reductions, Arm B	All Treated Subjects
3.1560	Summary of Adverse Events Leading to Dose Reductions, Arm C	All Treated Subjects
3.1570	Summary of Adverse Events Leading to Dose Delays, Arm A	All Treated Subjects
3.1580	Summary of Adverse Events Leading to Dose Delays, Arm B	All Treated Subjects
3.1590	Summary of Adverse Events Leading to Dose Delays, Arm C	All Treated Subjects
3.2010	Summary of Deaths, Arm A	All Treated Subjects
3.2020	Summary of Deaths, Arm B	All Treated Subjects
3.2030	Summary of Deaths, Arm C	All Treated Subjects
3.3110	Summary of Chemistry Toxicities by Maximum Grade, Arm A	All Treated Subjects
3.3120	Summary of Chemistry Toxicities by Maximum Grade, Arm B	All Treated Subjects
3.3130	Summary of Chemistry Toxicities by Maximum Grade, Arm C	All Treated Subjects
3.3140	Summary of Clinical Chemistry Grade Changes from Baseline Grade, Arm A	All Treated Subjects
3.3150	Summary of Clinical Chemistry Grade Changes from Baseline Grade, Arm B	All Treated Subjects
3.3160	Summary of Clinical Chemistry Grade Changes from Baseline Grade, Arm C	All Treated Subjects
3.3170	Summary of Clinical Chemistry Changes from Baseline With Respect to the Normal Range, Arm A	All Treated Subjects
3.3180	Summary of Clinical Chemistry Changes from Baseline With Respect to the Normal Range, Arm B	All Treated Subjects
3.3190	Summary of Clinical Chemistry Changes from Baseline With Respect to the Normal Range, Arm C	All Treated Subjects
3.3210	Summary of Hematology Toxicities by Maximum Grade, Arm A	All Treated Subjects
3.3220	Summary of Hematology Toxicities by Maximum Grade, Arm B	All Treated Subjects
3.3230	Summary of Hematology Toxicities by Maximum Grade, Arm C	All Treated Subjects
3.3240	Summary of Hematology Grade Changes from Baseline Grade, Arm A	All Treated Subjects
3.3250	Summary of Hematology Grade Changes from Baseline Grade, Arm B	All Treated Subjects
3.3260	Summary of Hematology Grade Changes from Baseline Grade, Arm C	All Treated Subjects
3.3270	Summary of Hematology Changes from Baseline With Respect to the Normal Range, Arm A	All Treated Subjects
3.3280	Summary of Hematology Changes from Baseline With Respect to the Normal Range, Arm B	All Treated Subjects
3.3290	Summary of Hematology Changes from Baseline With Respect to the Normal Range, Arm C	All Treated Subjects
3.3310	Summary of Urinalysis Dipstick Results, Arm A	All Treated Subjects
3.3320	Summary of Urinalysis Dipstick Results, Arm B	All Treated Subjects
3.3330	Summary of Urinalysis Dipstick Results, Arm C	All Treated Subjects

No.	Title	Population
3.4010	Summary of Vital Signs, Arm A	All Treated Subjects
3.4015	Summary of Vital Signs, Arm B	All Treated Subjects
3.4020	Summary of Vital Signs, Arm C	All Treated Subjects
3.4025	Summary of Change from Baseline Vital Signs, Arm A	All Treated Subjects
3.4030	Summary of Change from Baseline Vital Signs, Arm B	All Treated Subjects
3.4035	Summary of Change from Baseline Vital Signs, Arm C	All Treated Subjects
3.4040	Summary of Changes in Heart Rate from Baseline, Arm A	All Treated Subjects
3.4045	Summary of Changes in Heart Rate from Baseline, Arm B	All Treated Subjects
3.4050	Summary of Changes in Heart Rate from Baseline, Arm C	All Treated Subjects
3.4055	Summary of Increases in Systolic Blood Pressure from Baseline, Arm A	All Treated Subjects
3.4060	Summary of Increases in Systolic Blood Pressure from Baseline, Arm B	All Treated Subjects
3.4065	Summary of Increases in Systolic Blood Pressure from Baseline, Arm C	All Treated Subjects
3.4070	Summary of increases in Diastolic Blood Pressure from Baseline, Arm A	All Treated Subjects
3.4075	Summary of increases in Diastolic Blood Pressure from Baseline, Arm B	All Treated Subjects
3.4080	Summary of increases in Diastolic Blood Pressure from Baseline, Arm C	All Treated Subjects
3.4085	Summary of Changes in Temperature from Baseline, Arm A	All Treated Subjects
3.4090	Summary of Changes in Temperature from Baseline, Arm B	All Treated Subjects
3.4095	Summary of Changes in Temperature from Baseline, Arm C	All Treated Subjects
3.4110	Summary of ECOG Performance Status, Arm A	All Treated Subjects
3.4120	Summary of ECOG Performance Status, Arm B	All Treated Subjects
3.4130	Summary of ECOG Performance Status, Arm C	All Treated Subjects
3.4140	Summary of Change in ECOG Performance Status from Baseline, Arm A	All Treated Subjects
3.4150	Summary of Change in ECOG Performance Status from Baseline, Arm B	All Treated Subjects
3.4160	Summary of Change in ECOG Performance Status from Baseline, Arm C	All Treated Subjects
3.4210	Summary of Left Ventricular Ejection Fraction Change from Baseline, Arm A	All Treated Subjects
3.6010	Summary of ECG findings, Arm A	All Treated Subjects
3.6020	Summary of ECG findings, Arm B	All Treated Subjects
3.6030	Summary of ECG findings, Arm C	All Treated Subjects
3.6040	Summary of ECG Values, Arm A	All Treated Subjects
3.6050	Summary of ECG Values, Arm B	All Treated Subjects
3.6060	Summary of ECG Values, Arm C	All Treated Subjects
3.6070	Summary of Increases in QTcF, Arm A	All Treated Subjects
3.6080	Summary of Increases in QTcF, Arm B	All Treated Subjects
3.6090	Summary of Increases in QTcF, Arm C	All Treated Subjects

No.	Title	Population
3.6100	Summary of Amount of Increase from Baseline Value in QTc, Arm A	All Treated Subjects
3.6110	Summary of Amount of Increase from Baseline Value in QTc, Arm B	All Treated Subjects
3.6120	Summary of Amount of Increase from Baseline Value in QTc, Arm C	All Treated Subjects
3.8010	Summary of Liver Chemistry Assessments for Subjects with Liver Signal/Event, Arm A	All Treated Subjects
3.8020	Summary of Liver Chemistry Assessments for Subjects with Liver Signal/Event, Arm B	All Treated Subjects
3.8030	Summary of Liver Chemistry Assessments for Subjects with Liver Signal/Event, Arm C	All Treated Subjects
3.8040	Summary of Hepatobiliary Laboratory Abnormalities, Arm A	All Treated Subjects
3.8050	Summary of Hepatobiliary Laboratory Abnormalities, Arm B	All Treated Subjects
3.8060	Summary of Hepatobiliary Laboratory Abnormalities, Arm C	All Treated Subjects
3.8070	Summary of Liver Event Information for RUCAM Score, Arm A	All Treated Subjects
3.8080	Summary of Liver Event Information for RUCAM Score, Arm B	All Treated Subjects
3.8090	Summary of Liver Event Information for RUCAM Score, Arm C	All Treated Subjects
3.8100	Summary of Immunogenicity Binding Assay Results, Arm A	All Treated Subjects
3.8110	Summary of Immunogenicity Binding Assay Results, Arm B	All Treated Subjects
3.8120	Summary of Immunogenicity Binding Assay Results, Arm C	All Treated Subjects
3.8130	Summary of Titration Assay Results, Arm A	All Treated Subjects
3.8140	Summary of Titration Assay Results, Arm B	All Treated Subjects
3.8150	Summary of Titration Assay Results, Arm C	All Treated Subjects
3.16100	Summary of Characteristics of Adverse Event of Special Interest Bowel Perforation, Arm A	All Treated Subjects
3.16101	Summary of Characteristics of Adverse Event of Special Interest Cardiac Valve Fibrosis, Arm A	All Treated Subjects
3.16102	Summary of Characteristics of Adverse Event of Special Interest Infusion Related Reactions, Arm A	All Treated Subjects
3.16103	Summary of Characteristics of Adverse Event of Special Interest Hematologic Toxicities, Arm A	All Treated Subjects
3.16104	Summary of Characteristics of Adverse Event of Special Interest Nephrotoxicity, Arm A	All Treated Subjects
3.16105	Summary of Characteristics of Adverse Event of Special Interest Healing Abnormalities, Arm A	All Treated Subjects
3.16106	Summary of Characteristics of Adverse Event of Special Interest Hearing and Vestibular Disorders, Arm A	All Treated Subjects
3.16107	Summary of Characteristics of Adverse Event of Special Interest Hypothyroidism, Arm A	All Treated Subjects
3.16108	Summary of Characteristics of Adverse Event of Special Interest Ototoxicty, Arm A	All Treated Subjects
3.16109	Summary of Characteristics of Adverse Event of Special Interest Peripheral Neuropathy, Arm A	All Treated Subjects
3.16110	Summary of Characteristics of Adverse Event of Special Interest Bowel Perforation, Arm B	All Treated Subjects

No.	Title	Population
3.16111	Summary of Characteristics of Adverse Event of Special Interest Cardiac Valve Fibrosis, Arm B	All Treated Subjects
3.16112	Summary of Characteristics of Adverse Event of Special Interest Infusion Related Reactions, Arm B	All Treated Subjects
3.16113	Summary of Characteristics of Adverse Event of Special Interest Hematologic Toxicities, Arm B	All Treated Subjects
3.16114	Summary of Characteristics of Adverse Event of Special Interest Nephrotoxicity, Arm B	All Treated Subjects
3.16115	Summary of Characteristics of Adverse Event of Special Interest Healing Abnormalities, Arm B	All Treated Subjects
3.16116	Summary of Characteristics of Adverse Event of Special Interest Hearing and Vestibular Disorders, Arm B	All Treated Subjects
3.16117	Summary of Characteristics of Adverse Event of Special Interest Hypothyroidism, Arm B	All Treated Subjects
3.16118	Summary of Characteristics of Adverse Event of Special Interest Ototoxicty, Arm B	All Treated Subjects
3.16119	Summary of Characteristics of Adverse Event of Special Interest Peripheral Neuropathy, Arm B	All Treated Subjects
3.16120	Summary of Characteristics of Adverse Event of Special Interest Bowel Perforation, Arm C	All Treated Subjects
3.16121	Summary of Characteristics of Adverse Event of Special Interest Cardiac Valve Fibrosis, Arm C	All Treated Subjects
3.16122	Summary of Characteristics of Adverse Event of Special Interest Infusion Related Reactions, Arm C	All Treated Subjects
3.16123	Summary of Characteristics of Adverse Event of Special Interest Hematologic Toxicities, Arm C	All Treated Subjects
3.16124	Summary of Characteristics of Adverse Event of Special Interest Nephrotoxicity, Arm C	All Treated Subjects
3.16125	Summary of Characteristics of Adverse Event of Special Interest Healing Abnormalities, Arm C	All Treated Subjects
3.16126	Summary of Characteristics of Adverse Event of Special Interest Hearing and Vestibular Disorders, Arm C	All Treated Subjects
3.16127	Summary of Characteristics of Adverse Event of Special Interest Hypothyroidism, Arm C	All Treated Subjects
3.16128	Summary of Characteristics of Adverse Event of Special Interest Ototoxicty, Arm C	All Treated Subjects
3.16129	Summary of Characteristics of Adverse Event of Special Interest Peripheral Neuropathy, Arm C	All Treated Subjects
3.16200	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Bowel Perforation, Arm A	All Treated Subjects
3.16201	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Cardiac Valve Fibrosis, Arm A	All Treated Subjects
3.16202	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Infusion Related Reactions, Arm A	All Treated Subjects
3.16203	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hematologic Toxicities, Arm A	All Treated Subjects

No.	Title	Population
3.16204	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Nephrotoxicity, Arm A	All Treated Subjects
3.16205	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Healing Abnormalities, Arm A	All Treated Subjects
3.16206	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hearing and Vestibular Disorders, Arm A	All Treated Subjects
3.16207	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hypothyroidism, Arm A	All Treated Subjects
3.16208	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Ototoxicty, Arm A	All Treated Subjects
3.16209	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Peripheral Neuropathy, Arm A	All Treated Subjects
3.16210	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Bowel Perforation, Arm B	All Treated Subjects
3.16211	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Cardiac Valve Fibrosis, Arm B	All Treated Subjects
3.16212	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Infusion Related Reactions, Arm B	All Treated Subjects
3.16213	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hematologic Toxicities, Arm B	All Treated Subjects
3.16214	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Nephrotoxicity, Arm B	All Treated Subjects
3.16215	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Healing Abnormalities, Arm B	All Treated Subjects
3.16216	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hearing and Vestibular Disorders, Arm B	All Treated Subjects
3.16217	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hypothyroidism, Arm B	All Treated Subjects
3.16218	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Ototoxicty, Arm B	All Treated Subjects
3.16219	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Peripheral Neuropathy, Arm B	All Treated Subjects
3.16220	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Bowel Perforation, Arm C	All Treated Subjects
3.16221	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Cardiac Valve Fibrosis, Arm C	All Treated Subjects
3.16222	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Infusion Related Reactions, Arm C	All Treated Subjects
3.16223	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hematologic Toxicities, Arm C	All Treated Subjects
3.16224	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Nephrotoxicity, Arm C	All Treated Subjects
3.16225	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Healing Abnormalities, Arm C	All Treated Subjects

No.	Title	Population
3.16226	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hearing and Vestibular Disorders, Arm C	All Treated Subjects
3.16227	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Hypothyroidism, Arm C	All Treated Subjects
3.16228	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Ototoxicty, Arm C	All Treated Subjects
3.16229	Summary of Onset and Duration of the First Occurrence of Adverse Event of Special Interest Peripheral Neuropathy, Arm C	All Treated Subjects

20.1.5. Safety Figures

No.	Title	Population
13.0010	Plot of Duration of Study Treatment, Arm A	All Treated Subjects
13.0020	Plot of Duration of Study Treatment, Arm B	All Treated Subjects
13.0030	Plot of Duration of Study Treatment, Arm C	All Treated Subjects
13.0040	QTcF Shifts from Baseline to Worst-case Post Baseline, Arm A	All Treated Subjects
13.0050	QTcF Shifts from Baseline to Worst-case Post Baseline, Arm B	All Treated Subjects
13.0060	QTcF Shifts from Baseline to Worst-case Post Baseline, Arm C	All Treated Subjects
13.0070	Figure of LFT Patient Profiles for Possible Hy's Law Subjects, Arm A	All Treated Subjects
13.0080	Figure of LFT Patient Profiles for Possible Hy's Law Subjects, Arm B	All Treated Subjects
13.0090	Figure of LFT Patient Profiles for Possible Hy's Law Subjects, Arm C	All Treated Subjects
13.0100	Figure of Maximum Total Bilirubin vs Maximum ALT – eDISH Plot, Arm A	All Treated Subjects
13.0110	Figure of Maximum Total Bilirubin vs Maximum ALT – eDISH Plot, Arm B	All Treated Subjects
13.0120	Figure of Maximum Total Bilirubin vs Maximum ALT – eDISH Plot, Arm C	All Treated Subjects
13.0130	Trellis Display of Maximum versus Baseline LFT, Arm A	All Treated Subjects
13.0140	Trellis Display of Maximum versus Baseline LFT, Arm B	All Treated Subjects
13.0150	Trellis Display of Maximum versus Baseline LFT, Arm C	All Treated Subjects
13.0160	Matrix Display of Comparative LFT Scatter Plots, Arm A	All Treated Subjects
13.0170	Matrix Display of Comparative LFT Scatter Plots, Arm B	All Treated Subjects
13.0180	Matrix Display of Comparative LFT Scatter Plots, Arm C	All Treated Subjects
13.01900	Cumulative Incidence Plot of Bowel Perforation from Baseline	All Treated Subjects
13.01901	Cumulative Incidence Plot of Cardiac Valve Fibrosis from Baseline	All Treated Subjects
13.01902	Cumulative Incidence Plot of Infusiin Related Reactions from Baseline	All Treated Subjects
13.01903	Cumulative Incidence Plot of Nephrotoxicity from Baseline	All Treated Subjects
13.01904	Cumulative Incidence Plot of Hematologic Toxicities from Baseline	All Treated Subjects
13.01905	Cumulative Incidence Plot of Healing Abnormalities from Baseline	All Treated Subjects

No.	Title	Population
13.01906	Cumulative Incidence Plot of Hearing and Vestibular Disorders from Baseline	All Treated Subjects
13.01907	Cumulative Incidence Plot of Hypothyroidism from Baseline	All Treated Subjects
13.01908	Cumulative Incidence Plot of Ototoxicity from Baseline	All Treated Subjects
13.01909	Cumulative Incidence Plot of Peripheral Neuropathy from Baseline	All Treated Subjects

20.1.6. Pharmacokinetics Tables

No.	Title	Population
5.0010	Summary of GSK3052230 Plasma Pharmacokinetic Concentration-Time Data [ng/mL], Arm A	PK
5.0020	Summary of GSK3052230 Plasma Pharmacokinetic Concentration-Time Data [ng/mL], Arm B	PK
5.0030	Summary of GSK3052230 Plasma Pharmacokinetic Concentration-Time Data [ng/mL], Arm C	PK
5.0040	Summary of Paclitaxel Plasma Pharmacokinetic Concentration-Time Data [ng/mL], Arm A	PK
5.0050	Summary of Docetaxel Plasma Pharmacokinetic Concentration-Time Data [ng/mL], Arm B	PK
5.0060	Summary of Pemetrexed Plasma Pharmacokinetic Concentration-Time Data [ng/mL], Arm C	PK
5.1010	Summary of Derived GSK3052230 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed), Subjects with Extensive PK Sampling, Arm A	PK
5.1020	Summary of Derived GSK3052230 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed), Subjects with Extensive PK Sampling, Arm B	PK
5.1030	Summary of Derived GSK3052230 Plasma Pharmacokinetic Parameters (non-transformed and log-transformed), Subjects with Extensive PK Sampling, Arm C	PK

20.1.7. Pharmacokinetics Figures

Table No.	Title	Population
15.0010	Mean GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm A	PK
15.0020	Mean GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm B	PK
15.0030	Mean GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm C	PK

Table No.	Title	Population
15.0040	Mean GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm A	PK
15.0050	Mean GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm B	PK
15.0060	Mean GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm C	PK
15.0040	Median GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm A	PK
15.0050	Median GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm B	PK
15.0060	Median GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm C	PK
15.0070	Median GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm A	PK
15.0080	Median GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm B	PK
15.0090	Median GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm C	PK
15.1010	Box and Whisker Plot of Cycle 1 Day 8 GSK3052230 Pre-Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1020	Box and Whisker Plot of Cycle 2 Day 1 GSK3052230 Pre-Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1030	Box and Whisker Plot of Cycle 4 Day1 GSK3052230 Pre-Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1040	Box and Whisker Plot of Cycle 6 Day 1 GSK3052230 Pre-Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1050	Box and Whisker Plot of Cycle 12 Day 1 GSK3052230 Pre-Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1060	Box and Whisker Plot of Cycle 1 Day 8 End of GSK3052230 Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1070	Box and Whisker Plot of Cycle 2 Day 1 End of GSK3052230 Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK

Table No.	Title	Population
15.1080	Box and Whisker Plot of Cycle 4 Day1 End of GSK3052230 Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1090	Box and Whisker Plot of Cycle 6 Day 1 End of GSK3052230 Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.1091	Box and Whisker Plot of Cycle 12 Day 1 End of GSK3052230 Infusion Plasma Concentration at the Recommended Phase 2 Dose By Study Arm, Arms A, B, and C	PK
15.2010	Individual GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm A	PK
15.2020	Individual GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm B	PK
15.2030	Individual GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1 through C2D1, Subjects with Extensive PK Sampling, Arm C	PK
15.2010	Individual GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm A	PK
15.2020	Individual GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm B	PK
15.2030	Individual GSK3052230 Plasma Concentration-Time Plots (Linear and Semi-log) for C1D1, Subjects with Extensive PK Sampling, Arm C	PK

20.1.8. Pharmacodynamic Tables

No.	Title	Population
6.0010	Summary of FGFR1 Quantitative Measurements, Arm A	PD
6.0020	Summary of FGFR1 Quantitative Measurements, Arm B	PD
6.0030	Summary of FGFR1 Quantitative Measurements, Arm A&B	PD
6.0040	Summary of FGFR1 Amplification Rates, Arm A&B	PD

20.1.9. Pharmacodynamic Figures

Table No.	Title	Population
16.0010	Plot of FGFR1/CEP Ratio vs. Average FGFR1 Signial/Cell, Arm A&B	PD
16.0020	Plot of FGFR1/CEP Ratio vs. %Cells >/=5 FGFR1 Sig/Nucle, Arm A&B	PD
16.0030	Plot of Average FGFR1 Signals/Cell vs. %Cells >/=5 FGFR1 Sig/Nuclei, Arm A&B	PD
16.0040	Plot of Best Response by Average FGFR1 Signals, Arm A	PD

Table No.	Title	Population
16.0050	Plot of Best Response by Average FGFR1 Signals, Arm B	PD
16.0060	Plot of Best Response by FGFR1/CEP Ratio, Arm A	PD
16.0070	Plot of Best Response by FGFR1/CEP Ratio, Arm B	PD
16.0080	Plot of Best Response by Percentage of Cells >/=5 FGFR1 Sig/Nuclei, Arm A	PD
16.0090	Plot of Best Response by Percentage of Cells >/=5 FGFR1 Sig/Nuclei, Arm B	PD
16.0100	Plot of Duration of Treatment vs. Average FGFR1 Signals, Arm A	PD
16.0110	Plot of Duration of Treatment vs. Average FGFR1 Signals, Arm B	PD
16.0120	Plot of Duration of Treatment vs. FGFR1/CEP Ratio, Arm A	PD
16.0130	Plot of Duration of Treatment vs. FGFR1/CEP Ratio, Arm B	PD
16.0140	Plot of Duration of Treatment vs. Percentage of Cells >/=5 FGFR1 Sig/Nuclei, Arm A	PD
16.0150	Plot of Duration of Treatment vs. Percentage of Cells >/=5 FGFR1 Sig/Nuclei, Arm B	PD
16.0160	Plot of Progression Free Survival vs. Average FGFR1 Signals, Arm A	PD
16.0170	Plot of Progression Free Survival vs. Average FGFR1 Signals, Arm B	PD
16.0180	Plot of Progression Free Survival vs. FGFR1/CEP Ratio, Arm A	PD
16.0190	Plot of Progression Free Survival vs. FGFR1/CEP Ratio, Arm B	PD
16.0200	Plot of Progression Free Survival vs. Percentage of Cells >/=5 FGFR1 Sig/Nuclei, Arm A	PD
16.0210	Plot of Progression Free Survival vs. Percentage of Cells >/=5 FGFR1 Sig/Nuclei, Arm B	PD
16.0220	Plot of H-score by Best Response, Arm C	PD
16.0230	Plot of Duration of Treatment vs. H-score, Arm C	PD
16.0240	Plot of Progression Free Survival vs. H-score, Arm C	PD

20.1.10. ICH Listings

Section	Listing No.	Title	Population
Study Pop	21.0010	Listing of Planned and Actual Treatment, Arm A	All Treated Subjects
Study Pop	21.0020	Listing of Planned and Actual Treatment, Arm B	All Treated Subjects
Study Pop	21.0030	Listing of Planned and Actual Treatment, Arm C	All Treated Subjects
Study Pop	21.0040	Listing of Subjects Excluded from Analysis Populations, Arm A	All Screened Subjects
Study Pop	21.0050	Listing of Subjects Excluded from Analysis Populations, Arm B	All Screened Subjects
Study Pop	21.0060	Listing of Subjects Excluded from Analysis Populations, Arm C	All Screened Subjects
Study Pop	21.0070	Listing of Reasons for Study Withdrawal, Arm A	All Treated Subjects
Study Pop	21.0080	Listing of Reasons for Study Withdrawal, Arm B	All Treated Subjects
Study Pop	21.0090	Listing of Reasons for Study Withdrawal, Arm C	All Treated Subjects

Section	Listing No.	Title	Population
Study Pop	21.0100	Listing of Study Treatment Discontinuation Record, Arm A	All Treated Subjects
Study Pop	21.0110	Listing of Study Treatment Discontinuation Record, Arm B	All Treated Subjects
Study Pop	21.0120	Listing of Study Treatment Discontinuation Record, Arm C	All Treated Subjects
Study Pop	21.0130	Listing of Subjects with Inclusion/Exclusion Criteria Deviations, Arm A	All Treated Subjects
Study Pop	21.0140	Listing of Subjects with Inclusion/Exclusion Criteria Deviations, Arm B	All Treated Subjects
Study Pop	21.0150	Listing of Subjects with Inclusion/Exclusion Criteria Deviations, Arm C	All Treated Subjects
Study Pop	21.0160	Listing of Protocol Deviations, Arm A	All Treated Subjects
Study Pop	21.0170	Listing of Protocol Deviations, Arm B	All Treated Subjects
Study Pop	21.0180	Listing of Protocol Deviations, Arm C	All Treated Subjects
Study Pop	21.0190	Listing of Demographic Characteristics, Arm A	All Treated Subjects
Study Pop	21.0200	Listing of Demographic Characteristics, Arm B	All Treated Subjects
Study Pop	21.0210	Listing of Demographic Characteristics, Arm C	All Treated Subjects
Study Pop	21.0220	Listing of Race, Arm A	All Treated Subjects
Study Pop	21.0230	Listing of Race, Arm B	All Treated Subjects
Study Pop	21.0240	Listing of Race, Arm C	All Treated Subjects
Efficacy	22.0010	Listing of Investigator-Assessed Target Lesion Assessments (RECIST 1.1 Criteria), Arm A	All Treated Subjects
Efficacy	22.0020	Listing of Investigator-Assessed Target Lesion Assessments (RECIST 1.1 Criteria), Arm B	All Treated Subjects
Efficacy	22.0030	Listing of Investigator-Assessed Target Lesion Assessments (RECIST 1.1 Criteria), Arm C	All Treated Subjects
Efficacy	22.0040	Listing of Investigator-Assessed Target Lesion Assessments (Modified RECIST Criteria), Arm C	All Treated Subjects
Efficacy	22.0050	Listing of Investigator-Assessed Non Target Lesion Assessments (RECIST 1.1 Criteria), Arm A	All Treated Subjects
Efficacy	22.0060	Listing of Investigator-Assessed Non Target Lesion Assessments (RECIST 1.1 Criteria), Arm B	All Treated Subjects
Efficacy	22.0070	Listing of Investigator-Assessed Non Target Lesion Assessments (RECIST 1.1 Criteria), Arm C	All Treated Subjects
Efficacy	22.0080	Listing of Investigator-Assessed Non Target Lesion Assessments (Modified RECIST Criteria), Arm C	All Treated Subjects
Efficacy	22.0090	Listing of Investigator-Assessed New Lesions (RECIST 1.1 Criteria), Arm A	All Treated Subjects
Efficacy	22.0100	Listing of Investigator-Assessed New Lesions (RECIST 1.1 Criteria), Arm B	All Treated Subjects
Efficacy	22.0110	Listing of Investigator-Assessed New Lesions (RECIST 1.1 Criteria), Arm C	All Treated Subjects
Efficacy	22.0120	Listing of Investigator-Assessed New Lesions (Modified RECIST Criteria), Arm C	All Treated Subjects
Efficacy	22.0130	Listing of Investigator-Assessed Tumor Responses with confirmation (RECIST1.1 Criteria), Arm A	All Treated Subjects
Efficacy	22.0140	Listing of Investigator-Assessed Tumor Responses with confirmation (RECIST1.1 Criteria), Arm B	All Treated Subjects

Section	Listing No.	Title	Population
Efficacy	22.0150	Listing of Investigator-Assessed Tumor Responses with confirmation (RECIST1.1 Criteria), Arm C	All Treated Subjects
Efficacy	22.0160	Listing of Investigator-Assessed Tumor Responses with confirmation (Modified RECIST Criteria), Arm C	All Treated Subjects
Efficacy	22.0170	Listing of Progression-Free Survival, Arm A	All Treated Subjects
Efficacy	22.0180	Listing of Progression-Free Survival, Arm B	All Treated Subjects
Efficacy	22.0190	Listing of Progression-Free Survival, Arm C	All Treated Subjects
Safety	23.0010	Listing of Exposure to GSK3052230, Arm A	All Treated Subjects
Safety	23.0020	Listing of Exposure to GSK3052230, Arm B	All Treated Subjects
Safety	23.0030	Listing of Exposure to GSK3052230, Arm C	All Treated Subjects
Safety	23.0040	Listing of Exposure to Paclitaxel, Arm A	All Treated Subjects
Safety	23.0050	Listing of Exposure to Carboplatin, Arm A	All Treated Subjects
Safety	23.0060	Listing of Exposure to Docetaxel, Arm B	All Treated Subjects
Safety	23.0070	Listing of Exposure to Pemetrexed, Arm C	All Treated Subjects
Safety	23.0080	Listing of Exposure to Cisplatin, Arm C	All Treated Subjects
Safety	23.0090	Listing of Dose Reductions, Arm A	All Treated Subjects
Safety	23.0100	Listing of Dose Reductions, Arm B	All Treated Subjects
Safety	23.0110	Listing of Dose Reductions, Arm C	All Treated Subjects
Safety	23.0120	Listing of Dose Delays, Arm A	All Treated Subjects
Safety	23.0130	Listing of Dose Delays, Arm B	All Treated Subjects
Safety	23.0140	Listing of Dose Delays, Arm C	All Treated Subjects
Safety	23.0150	Listing of Missed Doses, Arm A	All Treated Subjects
Safety	23.0160	Listing of Missed Doses, Arm B	All Treated Subjects
Safety	23.0170	Listing of Missed Doses, Arm C	All Treated Subjects
Safety	23.0180	Listing of Incomplete Infusions, Arm A	All Treated Subjects
Safety	23.0190	Listing of Incomplete Infusions, Arm B	All Treated Subjects
Safety	23.0200	Listing of Incomplete Infusions, Arm C	All Treated Subjects
Safety	23.0210	Listing of Infusion Interruptions, Arm A	All Treated Subjects
Safety	23.0220	Listing of Infusion Interruptions, Arm B	All Treated Subjects
Safety	23.0230	Listing of Infusion Interruptions, Arm C	All Treated Subjects
Safety	23.0240	Listing of Dose Escalations, Arm A	All Treated Subjects
Safety	23.0250	Listing of Dose Escalations, Arm B	All Treated Subjects
Safety	23.0260	Listing of Dose Escalations, Arm C	All Treated Subjects
Safety	23.0270	Listing of the Relationship Between System Organ Class, Preferred Term, and Verbatim Text, Arm A	All Treated Subjects
Safety	23.0280	Listing of the Relationship Between System Organ Class, Preferred Term, and Verbatim Text, Arm B	All Treated Subjects
Safety	23.0290	Listing of the Relationship Between System Organ Class, Preferred Term, and Verbatim Text, Arm C	All Treated Subjects
Safety	23.0300	Listing of Subject Numbers for Individual Adverse Events, Arm A	All Treated Subjects
Safety	23.0310	Listing of Subject Numbers for Individual Adverse Events, Arm B	All Treated Subjects
Safety	23.0320	Listing of Subject Numbers for Individual Adverse Events,	All Treated Subjects

Section	Listing No.	Title	Population
		Arm C	
Safety	23.0330	Listing of All Adverse Events with Grade Change Details, Arm A	All Treated Subjects
Safety	23.0340	Listing of All Adverse Events with Grade Change Details, Arm B	All Treated Subjects
Safety	23.0350	Listing of All Adverse Events with Grade Change Details, Arm C	All Treated Subjects
Safety	23.0360	Listing of Fatal Serious Adverse Events, Arm A	All Treated Subjects
Safety	23.0370	Listing of Fatal Serious Adverse Events, Arm B	All Treated Subjects
Safety	23.0380	Listing of Fatal Serious Adverse Events, Arm C	All Treated Subjects
Safety	23.0390	Listing of Non-Fatal Serious Adverse Events, Arm A	All Treated Subjects
Safety	23.0400	Listing of Non-Fatal Serious Adverse Events, Arm B	All Treated Subjects
Safety	23.0410	Listing of Non-Fatal Serious Adverse Events, Arm C	All Treated Subjects
Safety	23.0420	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Arm A	All Treated Subjects
Safety	23.0430	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Arm B	All Treated Subjects
Safety	23.0440	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment, Arm C	All Treated Subjects
Safety	23.0450	Listing of Adverse Events Leading to Dose Delays, Arm A	All Treated Subjects
Safety	23.0460	Listing of Adverse Events Leading to Dose Delays, Arm B	All Treated Subjects
Safety	23.0470	Listing of Adverse Events Leading to Dose Delays, Arm C	All Treated Subjects
Safety	23.0480	Listing of Adverse Events Leading to Dose Reductions, Arm A	All Treated Subjects
Safety	23.0490	Listing of Adverse Events Leading to Dose Reductions, Arm B	All Treated Subjects
Safety	23.0500	Listing of Adverse Events Leading to Dose Reductions, Arm C	All Treated Subjects
Safety	23.0510	Listing of Dose-Limiting Adverse Events (DLTs), Arm A	All Treated Subjects
Safety	23.0520	Listing of Dose-Limiting Adverse Events (DLTs), Arm B	All Treated Subjects
Safety	23.0530	Listing of Dose-Limiting Adverse Events (DLTs), Arm C	All Treated Subjects
Safety	23.0540	Listing of Dose-Limiting Toxicities during the Determinative Period, Arm A	All Treated Subjects
Safety	23.0550	Listing of Dose-Limiting Toxicities during the Determinative Period, Arm B	All Treated Subjects
Safety	23.0560	Listing of Dose-Limiting Toxicities during the Determinative Period, Arm C	All Treated Subjects
Safety	23.05700	Listing of Adverse Event or Condition of Bowel Perforation, Arm A	All Treated Subjects
Safety	23.05701	Listing of Adverse Event or Condition of Cardiac Valve Fibrosis, Arm A	All Treated Subjects
Safety	23.05702	Listing of Adverse Event or Condition of Infusion Related Reactions, Arm A	All Treated Subjects
Safety	23.05703	Listing of Adverse Event or Condition of Hematologic Toxicities, Arm A	All Treated Subjects
Safety	23.05704	Listing of Adverse Event or Condition of Nephrotoxicity, Arm A	All Treated Subjects
Safety	23.05705	Listing of Adverse Event or Condition of Healing Abnormalities, Arm A	All Treated Subjects

Section	Listing No.	Title	Population
Safety	23.05706	Listing of Adverse Event or Condition of Hearing and Vestibular Disorders, Arm A	All Treated Subjects
Safety	23.05707	Listing of Adverse Event or Condition of Hypothyroidism, Arm A	All Treated Subjects
Safety	23.05708	Listing of Adverse Event or Condition of Ototoxicty, Arm A	All Treated Subjects
Safety	23.05709	Listing of Adverse Event or Condition of Peripheral Neuropathy, Arm A	All Treated Subjects
Safety	23.05710	Listing of Adverse Event or Condition of Bowel Perforation, Arm B	All Treated Subjects
Safety	23.05711	Listing of Adverse Event or Condition of Cardiac Valve Fibrosis, Arm B	All Treated Subjects
Safety	23.05712	Listing of Adverse Event or Condition of Infusion Related Reactions, Arm B	All Treated Subjects
Safety	23.05713	Listing of Adverse Event or Condition of Hematologic Toxicities, Arm B	All Treated Subjects
Safety	23.05714	Listing of Adverse Event or Condition of Nephrotoxicity, Arm B	All Treated Subjects
Safety	23.05715	Listing of Adverse Event or Condition of Healing Abnormalities, Arm B	All Treated Subjects
Safety	23.05716	Listing of Adverse Event or Condition of Hearing and Vestibular Disorders, Arm B	All Treated Subjects
Safety	23.05717	Listing of Adverse Event or Condition of Hypothyroidism, Arm B	All Treated Subjects
Safety	23.05718	Listing of Adverse Event or Condition of Ototoxicty, Arm B	All Treated Subjects
Safety	23.05719	Listing of Adverse Event or Condition of Peripheral Neuropathy, Arm B	All Treated Subjects
Safety	23.05720	Listing of Adverse Event or Condition of Bowel Perforation, Arm C	All Treated Subjects
Safety	23.05721	Listing of Adverse Event or Condition of Cardiac Valve Fibrosis, Arm C	All Treated Subjects
Safety	23.05722	Listing of Adverse Event or Condition of Infusion Related Reactions, Arm C	All Treated Subjects
Safety	23.05723	Listing of Adverse Event or Condition of Hematologic Toxicities, Arm C	All Treated Subjects
Safety	23.05724	Listing of Adverse Event or Condition of Nephrotoxicity, Arm C	All Treated Subjects
Safety	23.05725	Listing of Adverse Event or Condition of Healing Abnormalities, Arm C	All Treated Subjects
Safety	23.05726	Listing of Adverse Event or Condition of Hearing and Vestibular Disorders, Arm C	All Treated Subjects
Safety	23.05727	Listing of Adverse Event or Condition of Hypothyroidism, Arm C	All Treated Subjects
Safety	23.05728	Listing of Adverse Event or Condition of Ototoxicty, Arm C	All Treated Subjects
Safety	23.05729	Listing of Adverse Event or Condition of Peripheral Neuropathy, Arm C	All Treated Subjects
Safety	23.0580	Listing of Deaths, Arm A	All Treated Subjects
Safety	23.0590	Listing of Deaths, Arm B	All Treated Subjects
Safety	23.0600	Listing of Deaths, Arm C	All Treated Subjects
Safety	23.0610	Listing of Clinical Chemistry Data, Arm A	All Treated Subjects
Safety	23.0620	Listing of Clinical Chemistry Data, Arm B	All Treated Subjects
Safety	23.0630	Listing of Clinical Chemistry Data, Arm C	All Treated Subjects
Safety	23.0640	Listing of Hematology Data, Arm A	All Treated Subjects

Section	Listing No.	Title	Population
Safety	23.0650	Listing of Hematology Data, Arm B	All Treated Subjects
Safety	23.0660	Listing of Hematology Data, Arm C	All Treated Subjects
Safety	23.0670	Listing of Urinalysis Data, Arm A	All Treated Subjects
Safety	23.0680	Listing of Urinalysis Data, Arm B	All Treated Subjects
Safety	23.0690	Listing of Urinalysis Data, Arm C	All Treated Subjects
Safety	23.0700	Listing of ECOG Performance Status, Arm A	All Treated Subjects
Safety	23.0710	Listing of ECOG Performance Status, Arm B	All Treated Subjects
Safety	23.0720	Listing of ECOG Performance Status, Arm C	All Treated Subjects
PK	25.0010	Listing of Derived [Analyte] [Matrix] [Primary/Secondary] Pharmacokinetic Parameters {by Group}	PK
PK	25.1010	Listing of GSK3052230 Plasma Pharmacokinetic Concentration-Time Data, Arm A	PK
PK	25.1020	Listing of GSK3052230 Plasma Pharmacokinetic Concentration-Time Data, Arm B	PK
PK	25.1030	Listing of GSK3052230 Plasma Pharmacokinetic Concentration-Time Data, Arm C	PK
PK	25.1040	Listing of Paclitaxel Plasma Pharmacokinetic Concentration-Time Data, Arm A	PK
PK	25.1050	Listing of Docetaxel Plasma Pharmacokinetic Concentration-Time Data, Arm B	PK
PK	25.1060	Listing of Pemetrexed Plasma Pharmacokinetic Concentration-Time Data, Arm C	PK

20.1.11. Other Listings

Section	Listing No.	Title	Population
Study Pop	30.0010	Listing of Substance Use, Arm A	All Treated Subjects
Study Pop	30.0020	Listing of Substance Use, Arm B	All Treated Subjects
Study Pop	30.0030	Listing of Substance Use, Arm C	All Treated Subjects
Study Pop	30.0040	Listing of Current and Past Medical Conditions, Arm A	All Treated Subjects
Study Pop	30.0050	Listing of Current and Past Medical Conditions, Arm B	All Treated Subjects
Study Pop	30.0060	Listing of Current and Past Medical Conditions, Arm C	All Treated Subjects
Study Pop	30.0070	Listing of Disease Characteristics at Initial Diagnosis, Arm A	All Treated Subjects
Study Pop	30.0080	Listing of Disease Characteristics at Initial Diagnosis, Arm B	All Treated Subjects
Study Pop	30.0090	Listing of Disease Characteristics at Initial Diagnosis, Arm C	All Treated Subjects
Study Pop	30.0100	Listing of Disease Characteristics at Screening, Arm A	All Treated Subjects
Study Pop	30.0110	Listing of Disease Characteristics at Screening, Arm B	All Treated Subjects
Study Pop	30.0120	Listing of Disease Characteristics at Screening, Arm C	All Treated Subjects
Study Pop	30.0130	Listing of Metastatic Disease at Screening, Arm A	All Treated Subjects
Study Pop	30.0140	Listing of Metastatic Disease at Screening, Arm B	All Treated Subjects
Study Pop	30.0150	Listing of Metastatic Disease at Screening, Arm C	All Treated Subjects

Section	Listing No.	Title	Population
Study Pop	30.0160	Listing of Prior Anti-Cancer Chemotherapy, Hormonal, Immunotherapy, Small Molecule Targeted Therapy, Radioactive Therapy and Biologic Therapy, Arm B	All Treated Subjects
Study Pop	30.0170	Listing of Prior Anti-Cancer Chemotherapy, Hormonal, Immunotherapy, Small Molecule Targeted Therapy, Radioactive Therapy and Biologic Therapy, Arm C	All Treated Subjects
Study Pop	30.0180	Listing of Prior Anti-Cancer Radiotherapy, Arm B	All Treated Subjects
Study Pop	30.0190	Listing of Prior Anti-Cancer Radiotherapy, Arm C	All Treated Subjects
Study Pop	30.0200	Listing of Prior Surgical Procedures, Arm B	All Treated Subjects
Study Pop	30.0210	Listing of Concomitant Medications, Arm A	All Treated Subjects
Study Pop	30.0220	Listing of Concomitant Medications, Arm B	All Treated Subjects
Study Pop	30.0230	Listing of Concomitant Medications, Arm C	All Treated Subjects
Study Pop	30.0240	Listing of Blood Products, Arm A	All Treated Subjects
Study Pop	30.0250	Listing of Blood Products, Arm B	All Treated Subjects
Study Pop	30.0260	Listing of Blood Products, Arm C	All Treated Subjects
Study Pop	30.0270	Listing of Blood Supportive Care Products, Arm A	All Treated Subjects
Study Pop	30.0280	Listing of Blood Supportive Care Products, Arm B	All Treated Subjects
Study Pop	30.0290	Listing of Blood Supportive Care Products, Arm C	All Treated Subjects
Efficacy	30.0300	Listing of Investigator-Assessed Lesion Assessments (RECIST 1.1 Criteria), Arm A	All Treated Subjects
Efficacy	30.0310	Listing of Investigator-Assessed Lesion Assessments (RECIST 1.1 Criteria), Arm B	All Treated Subjects
Efficacy	30.0320	Listing of Investigator-Assessed Lesion Assessments (RECIST 1.1 Criteria), Arm C	All Treated Subjects
Efficacy	30.0330	Listing of Investigator-Assessed Lesion Assessments (Modified RECIST Criteria), Arm C	All Treated Subjects
Safety	30.0340	Listing of Abnormal ECG Findings, Arm A	All Treated Subjects
Safety	30.0350	Listing of Abnormal ECG Findings, Arm B	All Treated Subjects
Safety	30.0360	Listing of Abnormal ECG Findings, Arm C	All Treated Subjects
Safety	30.0370	Listing of ECG Values, Arm A	All Treated Subjects
Safety	30.0380	Listing of ECG Values, Arm B	All Treated Subjects
Safety	30.0390	Listing of ECG Values, Arm C	All Treated Subjects
Safety	30.0400	Listing of Vital Signs, Arm A	All Treated Subjects
Safety	30.0410	Listing of Vital Signs, Arm B	All Treated Subjects
Safety	30.0420	Listing of Vital Signs, Arm C	All Treated Subjects
Safety	30.0430	Listing of Left Ventricular Ejection Fraction Results, Arm A	All Treated Subjects
Safety	30.0440	Listing of Left Ventricular Ejection Fraction Results, Arm B	All Treated Subjects
Safety	30.0450	Listing of Left Ventricular Ejection Fraction Results, Arm C	All Treated Subjects
Safety	30.0460	Listing of Liver Chemistry Assessments for Subjects with Liver Signal/Events, Arm A	All Treated Subjects
Safety	30.0470	Listing of Liver Chemistry Assessments for Subjects with Liver Signal/Events, Arm B	All Treated Subjects

Section	Listing No.	Title	Population
Safety	30.0480	Listing of Liver Chemistry Assessments for Subjects with Liver Signal/Events, Arm C	All Treated Subjects
Safety	30.0490	Listing of Grouped Laboratory Tests and Grade -LFTs, Arm A	All Treated Subjects
Safety	30.0500	Listing of Grouped Laboratory Tests and Grade -LFTs, Arm B	All Treated Subjects
Safety	30.0510	Listing of Grouped Laboratory Tests and Grade -LFTs, Arm C	All Treated Subjects
Safety	30.0520	Listing of Grouped Laboratory Tests and Grade -Lipds, Arm A	All Treated Subjects
Safety	30.0530	Listing of Grouped Laboratory Tests and Grade -Lipds, Arm B	All Treated Subjects
Safety	30.0540	Listing of Grouped Laboratory Tests and Grade -Lipds, Arm C	All Treated Subjects
Safety	30.0550	Listing of Immunogenicity Assay Results, Arm A	All Treated Subjects
Safety	30.0560	Listing of Immunogenicity Assay Results, Arm B	All Treated Subjects
Safety	30.0570	Listing of Immunogenicity Assay Results, Arm C	All Treated Subjects
Safety	30.0580	Listing of Concurrent Actions Taken with Study Treatment Due to an Adverse Event, Arm A	All Treated Subjects
Safety	30.0590	Listing of Concurrent Actions Taken with Study Treatment Due to an Adverse Event, Arm B	All Treated Subjects
Safety	30.0600	Listing of Concurrent Actions Taken with Study Treatment Due to an Adverse Event, Arm C	All Treated Subjects
PD/Biomarker	26.0010	Listing of FGF2 Assay Results, Arm C	PD
PD/Biomarker	26.0020	Listing of FGF2 H-scores and Response, Arm C	PD

20.2. Appendix 2: Pharmacogenetics (PGx)

PGx – Background

Pharmacogenetics (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 pharmacokinetics (PK) (absorption, distribution, metabolism, and elimination), pharmacodynamics (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 associations with safety/adverse events include:

Drug	Disease	Gene	Outcome
Abacavir	HIV [Hetherington, 2002; Mallal, 2002]	Human Leukocyte Antigen B (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*1502* 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.
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 effectsA 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.

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 GSK3052230.

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 GSK3052230. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK3052230 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

In addition to any blood samples taken for the clinical study, a whole blood sample (~6 mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at the first opportunity after a subject has been randomized 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 only 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 GSK3052230 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 GSK3052230.

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

The aim of pharmacogenetic analyses will be to investigate the relationship between genetic variations in germline DNA and response to study treatment. The specific type of genetic investigation to be applied will be dependent on the most scientifically feasible approach available to address understanding of the response to the study treatment.

Generally, two approaches may be utilized to explore the association of genetic variation.

3. Candidate gene analysis where variations in specific genes may be studied that encode the drug target, or drug mechanism of action pathways, drug metabolizing enzymes, drug transporters or which may underpin adverse events, disease risk or drug response.

These 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 GSK3052230. The genes that may code for these proteins may also be studied.

4. 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 A detailed description of the analyses to be performed will be documented in the pharmacogenetics 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 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 clinical study report,.

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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