The GlaxoSmithKline group of companies 205801

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for a Phase II, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants
Compound Number	:	GSK3359609
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned final analyses and outputs for each substudy in the Clinical Study Report (CSR) for 205801. Separate CSRs will be produced for each substudy.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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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:

Revision Chronology:		
2017N337080_00	23-JUL-2018	Original
2017N337080_01	20-SEP-2018	Amendment No.1 Protocol was amended at the request of the regulatory authority to provide additional clarification and guidance on specific aspects of the protocol
2017N337080_02	15-JUL-2019	Amendment No.2 Protocol was amended based on regulatory and ethics committee feedback to provide additional clarification and guidance on specific aspects of the protocol as described in the table in the protocol
2017N337080_03	29-OCT-2020	Amendment No.3 . Protocol was amended to add new substudies
TMF-11698443	02-FEB-2021	Amendment No. 4. Protocol was amended to change the primary analysis criteria.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 4 (Dated: 02/FEB/2021).

2.2. Study Objective(s) and Endpoint(s)

Part 1:

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To determine the safety and tolerability of novel regimens	• AEs, SAEs, DLTs, changes in safety/laboratory assessment parameters, dose modifications
Secondary Objectives	**Secondary Endpoints**
• To provide a preliminary evaluation of the efficacy of feladilimab in combination with novel regimens	• Objective Response Rate (ORR) • Disease Control Rate (DCR)
• Characterize the pharmacokinetic properties of feladilimab (ICOS Agonist) or investigational feladilimab combination partners	• PK parameters that include Cmax and Cmin for feladilimab and in combination (and investigational agent/s included in other arms), as data permit.

Objectives	Endpoints
Exploratory Objectives	**Exploratory Endpoints**
CCI [redacted]	

Part 2:

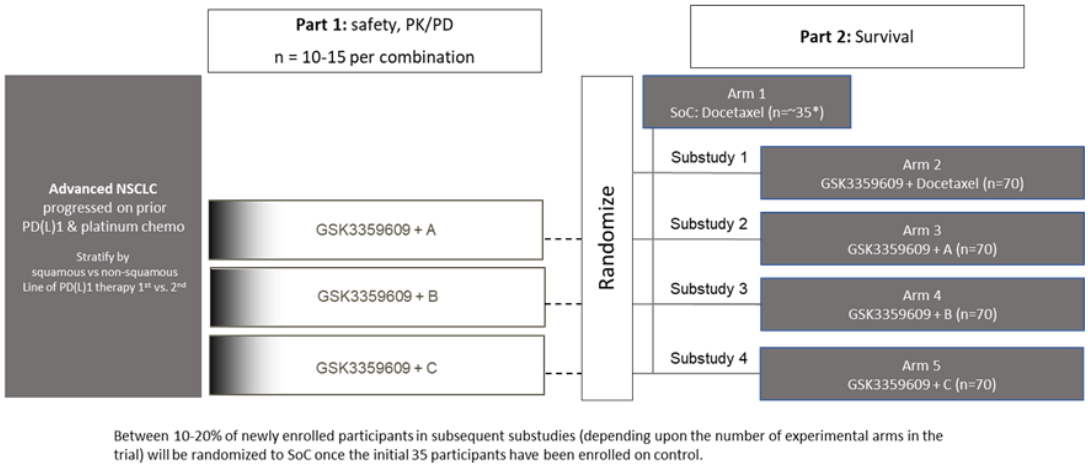
Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• Determine whether experimental regimens provide evidence for improved survival over SoC therapy	• Overall survival as measured by time from randomization to death
Secondary Objectives	**Secondary Endpoints**
• Evaluate milestone survival in participants treated with experimental regimens versus SoC therapy for NSCLC	• Milestone survival rate at 12 and 18 months
• Evaluate other measures of antitumor activity of the experimental regimens compared with SoC therapy for NSCLC (RECIST 1.1 and iRECIST)	• CR, PR, SD, PD, PFS, ORR, DOR, DCR iCR, iPR, iUPD, iCPD, iSD iPFS; iORR; iDOR
• Evaluate the safety and tolerability of the experimental regimens compared with SoC therapy for NSCLC	• Frequency and severity of AEs, AESI; SAEs and AE/SAEs leading to dose modifications/delays/withdrawals; changes in laboratory, vital signs, and safety assessment parameters, including immunogenicity (ADA)
• Characterize the pharmacokinetic properties of feladilimab /SoC, or investigational feladilimab combination partners	• PK parameters that may include Cmax and Cmin for feladilimab and SoC in combination (and investigational agent/s included in other arms) and for SoC alone, as data permit..
• Determine immunogenicity of experimental regimens	• ADA incidence for feladilimab and combination partners (where appropriate)
Exploratory Objectives	**Exploratory Endpoints**
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

Note: The prefix "i",used for response related abbreviations in the above table indicates immune responses assigned using iRECIST.

2.3. Study Design

Overview of Study Design and Key Features



Between 10-20% of newly enrolled participants in subsequent substudies (depending upon the number of experimental arms in the trial) will be randomized to SoC once the initial 35 participants have been enrolled on control.

ICOS: Inducible T-Cell Co-Stimulator; NSCLC: non-small cell lung cancer; PD(L)1: Programmed Cell Death Protein 1 or Programmed Cell Death Ligand 1.

Note: Randomization of participants to experimental treatment regimens/arms may not occur in parallel. It should also be noted that the terms 'regimen' and 'arm' may be used interchangeably throughout the document.

Design Features	• A randomized, open-label, platform trial utilizing a master protocol • The study is structured as a series of substudies that share a common control arm • The study has 2 parts, i.e. part 1 and part 2. • Part 1 is a non-randomized part based on safety and pharmacokinetics/pharmacodynamics (PK/PD) evaluation. • Part 2 is a randomized, Phase II part comparing the efficacy and safety of these novel regimens with SoC. • Sub-study 1 has only part 2 and subsequent sub-studies (sub-studies 2,3 and 4) have both part 1 and 2 • Additional regimens may be added based on emerging nonclinical and clinical data, via future protocol amendment(s). This RAP will be upated as new arms are added. • The study will evaluate the efficacy of feladilimab (ICOS Agonist) in combination with other treatment regimens compared with SoC (docetaxel) alone as the standard subsequent line chemotherapy Within Part 2 of each sub-study, patients will be randomized to receive either SoC or the experimental treatment; the randomisation ratios may change depending on the number of sub-studies running in parallel. • Additional treatment arms may be added as sub-studies via future protocol amendments, and ongoing treatment arms may be dropped based on interim OS results or emerging safety information

Overview of Study Design and Key Features

Dosing

Sub-study	Treatment Arm	Dosage	Route of Administration	Dosing Frequency
SoC	Docetaxel	75 mg/m^2	IV infusion	Once Q3W
Sub-study 1	feladilimab	80 mg	IV infusion	Once Q3W
	Docetaxel	75 mg/m^2	IV infusion	Once Q3W
Sub-study 2	Ipilimumab	1 mg/kg 3 mg/kg	IV infusion	Once Q3W
	feladilimab	24mg	IV infusion	Once Q3W
Sub-study 3	Niraparib	200 mg[a] 300 mg[b]	Oral	Daily
	feladilimab	24mg	IV infusion	Once Q3W
Sub-study 4	Dostarlimab	500 mg	IV infusion	Once Q3W
	Cobolimab	300 mg	IV infusion	Once Q3W
	feladilimab	24mg	IV infusion	Once Q3W

a: For participants with a baseline body weight <77 kg or baseline platelet count <150,000/µL.
b: For participants with baseline body weight ≥77 kg and baseline platelet count ≥150,000/µL.

- Experimental treatment (combination) will continue to be administered at the indicated schedule with the maximum duration as specified in the protocol for each combination arm, or until disease progression as determined by iRECIST, death, unacceptable toxicity, or other protocol-defined criteria are met.
- Single agent SoC treatment may continue until disease progression, death, unacceptable toxicity, withdrawal of consent, or per insitiutional standard for docetaxel.

Time & Events

- [Refer to Appendix 2: Schedule of Activities]

Treatment Assignment

At study start, participants will be randomized 1:2 to Arm 1 (SoC) and Arm 2, i.e., 33% and 67%, respectively. Between 10-20% of newly enrolled participants in subsequent sub-studies (depending upon the number of experimental arms in the trial) will be randomized to SoC once the initial 35 participants have been enrolled on control. Once determined to be eligible for the study, all participants will be centrally randomized using RAMOS, an Interactive Web Response System (IWRS).

Interim Analysis

- No interim analysis is involved in part 1
- In part 2, interim analyses focusing on safety (also including OS) will be performed approximately every 3 to 6 months depending on the amount of additional data accrued. These interims would be conducted across all substudies, reported by treatment and SoC will be combined across all substudies.

Overview of Study Design and Key Features	
	• An interim analysis of OS will be conducted for each experimental arm after approximately 45 events (experimental arm and SoC combined) and a minimum of 18 events from experimental arm have been observed. • Interim analysis will assess futility. Success will only be declared at the final analysis. • Interim analysis will be performed by an independent third party Statistical Data Analysis Center (SDAC) and details of Interim Analysis Plan will not be described in this document but will be described in SDAC Reporting Plan (Section 12.12)

2.4. Statistical Hypotheses / Statistical Analyses

2.4.1. Hypothesis

Part 1: The primary objective of Part 1 is to establish the safety and tolerability of the experimental combination regimen of each substudy.

Part 2:

The primary objective of the study is to determine whether the experimental arms prolong overall survival relative to standard of care (SoC).
The null hypothesis is that there is no difference in overall survival between each experimental arm and the SoC and alternative hypothesis is that the experimental regimen improves overall survival over the SoC. No comparisons will be made between experimental arms.
The predictive probability inference approach will be used as the basis for both interim and final success decision making. The predictive probability of Phase III study success (defined as a statistically significant log-rank test with1-sided alpha=0.025) will be calculated as a measure of the improvement in OS in the experimental arm compared with the SoC arm.
As this is a signal finding study and not confirmatory, each experimental arm will be compared to control in a pairwise fashion with no adjustment for multiple comparisons.

2.4.2. Sample Size

Part 1:

A maximum of 15 participants will be enrolled to each scheduled regiment in Part 1.

Part 2:

In Part 2, 70 participants in each experimental arm and a minimum of 35 participantes in the SoC arm will be randomized. Sample size and associated operating characteristics were evaluated via simulation.

The 8-month milestone survival in the SoC arm is estimated to be ~40% in advanced squamous cell lung cancer (Brahmer, 2015), ~60% in advanced non-squamous lung cancer (Borghaei, 2015), and ~50% in PD-L1 positive population (Herbst, 2016). The participant population in the current study is expected to be a mixed population with both squamous and nonsquamous lung cancer participants; therefore, mean target rate is assumed to be ~50% (Figure 1).

For the target effect of experimental regimens, there is a potential delayed effect at treatment start and sustained effect after prolonged follow-up (Brahmer, 2015; Borghaei, 2015). The survival probability in these arms is expected to overlap that in the SoC arm for up to 4 months from start of treatment followed by a separation. It is hypothesized that percentage of surviving participants is maintained at 20% after 24 months (Figure 1).

Under the alternative hypothesis, three-piece piecewise Weibull distributions are used to describe the survival distribution of each experimental arm and two-piece piecewise Weibull distributions are used to describe the survival curve of docetaxel (Table 48 in Section 12.13.1 of the protocol describes the simulation parameters). Using this modelling approach for the primary endpoint of OS, the assumed survival curve for the SoC arm is presented using blue dashes and the target survival curve for the experimental arm is presented as the solid red curve in Figure 1. Based on these two curves, the hazard ratio is approximately 0.58.

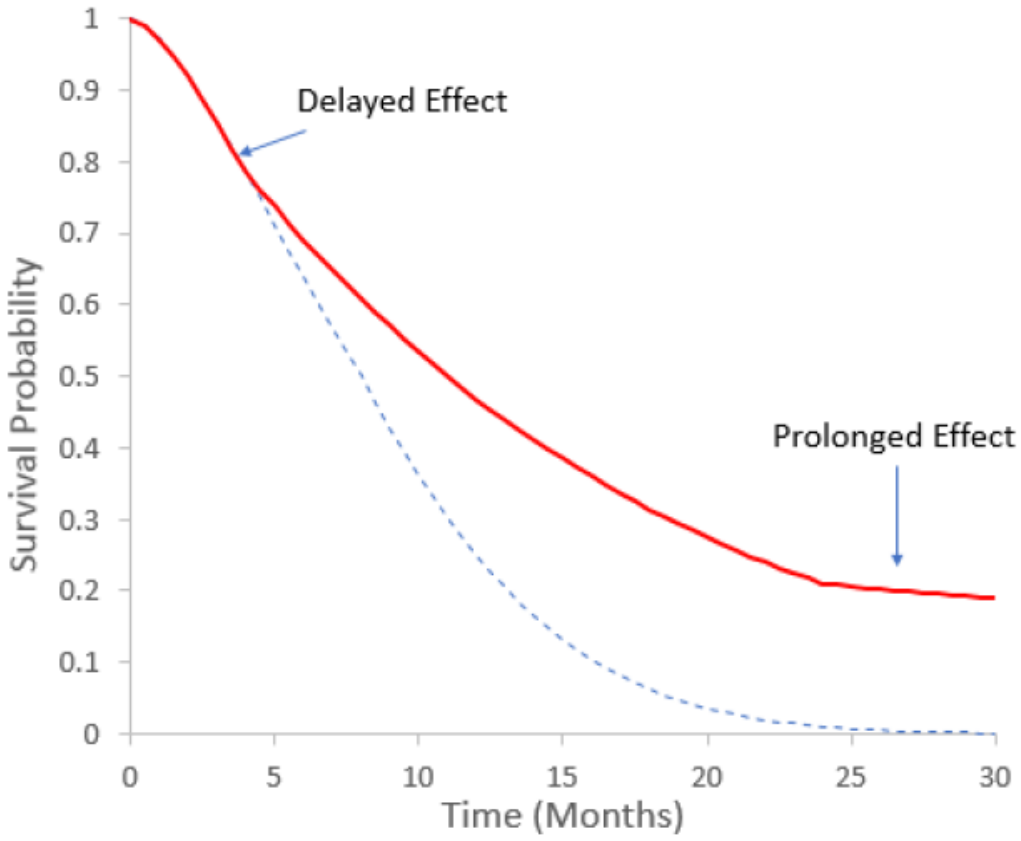
Sample size was chosen by simulating the a study in which 4 experimental arms enter the master protocol at different points in time. Enrollment of 9 participants per month is assumed. Interim and final analyses are performed based on predetermined decision rules as specified in Section 3. The planned Phase III sample size is 300 (150 participants per arm and a total of 210 events). The future phase 3 trial will use the log-rank (frequentist) test and the decision rule at interim and end of phase 2 will use the (Bayesian) predictive probability, given the results in phase 2, that the future log-rank test in phase 3 will be significant, thus, resulting in a methodology that is a mixture of Bayesian and frequentist. Simulations assess the Operating Characteristics of the predictive probability decision criteria under the null and alternative hypotheses. A cutoff of 43% or greater for the predictive probability of phase 3 success is used to define success for each experimental arm. Sample size was calculated under the simulated survival curves shown below (Figure 1).

The final analysis of OS for a substudy will be performed when approximately 85 death events have occurred in the experimental arm and SoC arm combined, and the last participant in that substudy has been randomized for at least 6 months. In the case death events occur at a rate lower than expected due to potentially prolonged survival benefit, to avoid substantial delay of final analysis for a substudy, the primary analysis for a substudy may be conducted once approximately 75 events have occurred and the last participant in that substudy has been randomized for at least 6 months, at the discretion of the Sponsor. A minimum of 35 events are needed from the experimental arm for both primary and final analysis.

Assuming the true HR≈0.58, 85 death events will provide 94.2% probability (power) of achieving the predictive probability success criteria for future phase 3 success of ≥ 43%.

In the case of primary analysis being performed with 75 death events, it will provide 88.3% probability of achieving the predictive probability success criteria. If the true HR is 1, 85 and 75 death events will provide 16.6% and 18.2% probability of achieving the predictive probability success criteria (Type I error), respectively

Figure 1 Assumed Survival Probability Under Alternative Hypothesis in Experimental Regimnes (Red) and Docetaxel (Blue)



3. PLANNED ANALYSES

3.1. Interim Analyses

Part 1:

No interim analysis will be performed in part 1 of the study

Part 2:

This is a platform study utilizing a master protocol designed so that experimental arms may enter and leave the trial independently at different time points as determined by pre-specified decision criteria. This study will be conducted under the auspices of an IDMC and Steering Committee. The IDMC will review all available interim safety and efficacy (OS only) data as the study progresses. The details of the data that will be reviewed by IDMC is described in the IDMC charter and/or the SDAC Reporting Plan (Section 12.12). The Steering Committee will provide guidance over key decision points during the conduct of the study including, but not limited to, the introduction of new experimental arms into the master protocol, graduation of existing arms for further development in other studies, and end of study. The SoC may be changed during the course of the study and this may require update to the RAP and study protocol.

Interim analyses will be performed approximately every 3 to 6 months depending on the amount of additional data accrued.

For each experimental arm, an interim analysis of OS will be performed. The study may be stopped for futility at this interim analysis.

3.1.1. Interim Analyses for Overall Survival (OS)

Interim Analysis will be performed by Statistical Data Analysis Center (SDAC) for IDMC.

OS is defined as the interval from date of randomization to the date of death, irrespective of the cause of death. If a participant does not have a documented date of death or is lost to follow-up, time of death will be censored at the date of last contact.

An interim analysis of OS will be conducted for each experimental arm after approximately 45 events (experimental arm and SoC combined) and a minimum of 18 events from experimental arm have been observed. Interim analyses will not be used to declare success of any experimental arm.

The study will employ a Bayesian decision-making framework based on the predictive probability of observing a significant improvement in OS in a future Phase III trial. The predictive probability inference approach will be used as the basis for interim analyses. The predictive probability of Phase III study success (defined as a statistically significant improvement in OS, 1-sided alpha=0.025) will be calculated as a measure of the improvement in OS in the experimental arm compared with the SoC arm. Each experimental arm will be compared to the SOC arm in a pairwise fashion with no adjustment for multiple comparisons.

If the predictive probability of phase 3 success for a particular experimental arm is very low (as defined in the IDMC charter and/or SDAC Reporting Plan (Section 12.12), that experimental arm may be considered for termination. Final decision on termination of an experimental arm will be based on the totality of the data, which will include the calculated predictive probability of success and the available safety data for that experimental arm.

3.2. Primary and Final Analyses

The final planned primary analyses for each experimental arm will be performed after the completion of the following sequential steps:

Part 1:

1. A futility analysis of ORR will be conducted after 10 participants have had at least two post baseline RECIST assessments.

2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

3. Randomization codes have been distributed according to RandAll NG.

Part 2:

1. The final analysis for each experimental arm will occur after observing approximately 85 events (experimental regimen and SoC combined) with minimum of 35 events in the experimental arm.

2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.

3. Randomization codes have been distributed according to RandAll NG.

The rest of the data on remaining subjects will be reported appropriately at study end. The RAP will be updated accordingly for each sub study.

In the case death events occur at a rate slower than expected due to potentially prolonged survival benefit, to avoid substantial delay of final analysis for a substudy, primary analysis for a substudy may be conducted once approximately 75 events have occurred and at least 35 events observed in the experimental arm, and the last participant in that substudy has been randomized for at least 6 months, at the discretion of the Sponsor.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Safety	• All randomized participants who received at least one dose of SoC or experimental regimen based on actual treatment received.	• Safety
Intent-To-Treat (ITT)	• All participants who were randomized to treatment regardless of whether the participants actually received study treatment.	• Study Population • Efficacy
Pharmacokinetic (PK)	• All participants in the safety population from whom at least one blood sample was obtained and analysed for PK concentration.	• PK Concentration and PK parameters
DLT Evaluable	• A subset of participants in part 1 who have received the first course of treatment containing both agents within a sub-study and followed up for a 21-day period or withdrawn within 21 days due to an AE meeting the definition of a DLT. • For oral dosing, a participant is considered DLT evaluable if they received at least 80% the first course of treatment containing both agents within a sub-study and followed up for a 21-day period or withdrawn within 21 days due to an AE meeting the definition of a DLT	• DLT

Refer to Appendix 10 : List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important and non-important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and important protocol deviations will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		**Data Displays for Reporting**	
Code	**Description**	**Description**	**Order in TFL**
S	Standard of Care Docetaxel 75 mg/m2	Docetaxel	1
A	GSK3359609 (ICOS Agonist) 80 mg plus docetaxel (Treatment Regimen 1)	GSK3359609 80 mg plus Docetaxel 75 mg/m2	2
E	GSK3359609 (ICOS Agonist) plus 1 mg/kg Ipilimumab (Treatment Regimen 2)	Feladilimab 24 mg plus Ipilimumab 1 mg/kg	2
F	GSK3359609 (ICOS Agonist) plus 3 mg/kg Ipilimumab (Treatment Regimen 3)	Feladilimab 24 mg plus Ipilimumab 3 mg/kg	3
G	GSK3359609 (ICOS Agonist) plus Niraparib (Treatment Regimen 4)	Feladilimab 24 mg plus Niraparib	2
H	GSK3359609 (ICOS Agonist) plus Dostarlimab plus Cobolimab (Treatment Regimen 5)	Feladilimab 24 mg plus Dostarlimab 500 mg plus Cobolimab 300 mg	2

5.2. Baseline Definitions

- For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. For laboratory data, baseline will be the latest non-missing pre-dose value from local lab will be used.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

In this multicentre and multi-country study, enrolment will be presented by country and investigative site. All centres will be pooled prior to analysis.

Additional displays on specific region may be explored as data warrants.

5.4. Examination of Covariates, Other Strata and Subgroups

Part 1:

No stratification and subgroup analysis is performed in part 1.

Part 2:

5.4.1. Covariates and Other Strata

The list of covariate and strata described below may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses if data permits. Additional covariates and other strata of clinical interest may also be considered as data warrants.

Category	Details
Strata	Squamous vs. Non-squamous Line of PD(L)1 therapy 1st vs. 2nd

5.4.2. Examination of Subgroups

Subgroups may be explored as the study progresses. Subgroup analysis may be performed if data permits. In addition to the strata listed above, subgroups of interest may include Gender and Age.

Subgroup	Categories
Gender	Male; Female
Age	<65; ≥65

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5.5. Multiple Comparisons and Multiplicity

Each experimental arm will be compared to control in a pairwise fashion with no adjustment for multiple comparisons. No formal comparisons will be made between experimental arms.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the ITT, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, past and current medical conditions, prior and concomitant medications, disease characteristics at initial diagnosis and at screening, prior and follow-up anti-cancer therapy, surgical/medical procedures, substance use, duration of follow up, will be based on GSK Core and Oncology Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

6.2. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 4 will be provided. Number of subjects based on the ITT will be summarized by country and site for each cohort.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who have completed the study or have withdrawn from the study, including primary and secondary (if any) reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF (Electronic Case Report Form). Subjects who die for any reason during on-treatment period will be considered to have completed the study.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who 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 treatment discontinuation will be generated. The listing will include last dose date and primary reasons for study treatment discontinuation.

The number and percentage of subjects who passed screening and entered the study, who failed screening and therefore were not entered into the study, and subjects who met eligibility criteria but were not needed will be summarized along with the reasons for failure will be summarized for those subjects who failed screening. A subject may have more than one reason for screen failure.

Since screen failures are not assigned to treatment groups, the display has only one subject-group column regardless of study design. Also, since screen failures cannot be attributed to any of the sub-studies repeat reporting may occur in different sub-studies/parts. This summary will be based on the Screened population.

The number of subjects will be summarized by Country, Site ID and Investigator ID. This summary must be produced based on the all enrolled population. The total column, summarizing subjects regardless of treatment, should always be included. Rows should be sorted alphabetically by country, then in numerical order by Site ID

6.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, height, and baseline body weight) will be listed and summarized. Age, height and weight will be summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized by 18-64, 65-74, 75-84, and ≥85. The count and percentage will be computed for race, ethnicity and sex.

A separate summary of age ranges based on the ITT population will be provided. Age will be summarized in categories: 18-64, 65-84, and ≥85. Race and racial combinations will also be summarized. Listing of Race will also be provided.

6.4. Prior Medical Condition and Disease Characteristics

Disease history and characteristics (primary tumor type, lesion status, time since initial diagnosis, stage at initial diagnosis, time since last progression) will be summarized. Indicators (yes/no) for the following, collected at screening, will also be summarized: measurable disease, non-target lesions, and metastatic disease. Medical conditions present at screening will be listed and will be summarized by past and current. Disease history and characteristics, as well as these medical conditions, will be presented in data listings.

A summary of disease burden at baseline will be provided. Information on sites of metastatic disease at screening will be summarized.

Prior cancer related surgeries will be summarized and listed.

6.5. Prior and Subsequent Anti-cancer Therapy

Anti-cancer therapy will be coded using GSK Drug dictionary version 1.6 or higher. Prior anti-cancer therapy will be coded using GSK Drug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between Anatomical Therapeutic Chemical (ATC) Level 1, ingredient, and verbatim text; therapies will be classified by type (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy,surgery and radiotherapy).

ATC classification Level 1 (Body System) information will be included in the dataset created but will not appear on the listing or summary.

The prior and follow-up anti-cancer therapies will be summarised by ingredient. The number and percentage of subjects that received different types of anti-cancer therapies ((chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy,surgery and radiotherapy) as prior therapy and

follow-up therapy will be summarised separately. A subsequent listing of the type of Anti-cancer therapy received will be provided with an indicator variable(Yes/No) for Prior and Follow-up anti-cancer therapy and prior radio therapy

6.6. Concomitant Medications

Prior medications will be coded using GSK Drug coding dictionary and summarized. The summary of prior medications will show the number and percentage of subjects taking prior medications by Ingredient.

Concomitant medications will be coded using GSK Drug coding dictionary and summarized. 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.

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

Concomitant medications will be summarized separately for medications with onset date within the on-therapy period and for medications with onset date within the pre-therapy period. Note: In order to be considered a concomitant medication, the concomitant medication must have been taken at some point during the on-therapy window.

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 treatment will be provided. Supportive listings will also be provided.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

There is no primary efficacy analysis or endpoint for Part 1.

The primary efficacy analyses for Part 2 will be based on the ITT population, unless otherwise specified and all summaries and data listings will use treatment labels as specified in Section 5.1.

Primary endpoint is OS and primary analysis is based on the predictive probability of Phase III study success.

Overall Survival (OS) is defined as the time from randomization to the date of death for any cause. In the absence of confirmation of death, survival time will be censored at the last date the subject is known to be alive (i.e., at their last known alive date from long term follow-up).
The length of OS will be calculated as

OS = death date or last known alive date – date of randomisation + 1

Subjects lacking data beyond date of randomisation will have their survival times censored at date of randomisation.

7.1.2. Summary Measure

Hazard Ratio for OS will be estimated using the cox proportional hazard model stratified by the histology(squamous vs. non-squamous) and line of PD-L1 therapy(1st line vs. 2nd line) with treatment arm as the sole explanatory variable.

The distribution of OS for each treatment arm will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of OS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982).

7.1.3. Population of Interest

The primary efficacy analyses will be based on the ITT population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Not applicable

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

Endpoint / Variables
• OS
Model Specification
• Hazard ratio for OS and corresponding 95% confidence interval will be estimated using the Cox's proportional hazard model stratified by stratified by the histology(squamous vs. non-squamous) and line of PD-L1 therapy(1st line vs. 2nd line) with treatment arm as the sole explanatory variable. • The predictive probability of Phase III study success (defined as a statistically significant log-rank test with 1-sided alpha=0.025) will be calculated as a measure of the improvement in OS in the experimental arm compared with the SoC arm. • The predictive probability of success in a future Phase III study will be calculated using the posterior predictive distribution of log(HR in phase 3), given log(HR from phase 2), assuming that both the observed log(HR) and prior for mean of log(HR) follow normal distributions as outlined below. • Let us assume that the prior of hazard ratio (in logarithm scale) follows normal distribution with mean as θ_0 and a standard deviation of sqrt($4/n_0$) $$\theta \sim N(\theta_0, V_0)$$ where $V_0 \sim 4/n_0$, n_0 = some number that could be interpreted as the number of events in a trial where the prior information came from; a small value corresponds to a large variance for the prior distribution and thus, the prior is considered non-informative. The expression for the variance comes from (Parmar, 1998) if the trial where the prior info was obtained has equal sample size allocation between the 2 groups. • The posterior distribution is also normal (Gelman, 2013) and is given by: $$\theta | x \sim N\left(\frac{V_0}{V_{p2}+V_0}x + \frac{V_{p2}}{V_{p2}+V_0}\theta_0, \frac{1}{1/V_0 + 1/V_{p2}}\right).$$ • The *posterior* predictive distribution, given the observed data in phase 2, is normal (Gelman, 2013) and is of the form $$y|(X=x) \sim N\left(\frac{V_0}{V_{p2}+V_0}x + \frac{V_{p2}}{V_{p2}+V_0}\theta_0, \frac{1}{1/V_0 + 1/V_{p2}} + V_{p3}\right)$$

$$where\ V_{p3} = V\left[\log\left(\widehat{HR}_{p3}\right)\right]$$

- and V_{p3} is assumed to be known. If the numerator and denominator of the expression for the mean is divided by $(V_0 V_{p2})$, the posterior predictive distribution is of the form

$$Y|x \sim N\left(\frac{\frac{V_0}{V_0 V_{p2}}}{\frac{V_{p2}}{V_0 V_{p2}} + \frac{V_0}{V_0 V_{p2}}} x + \frac{\frac{V_{p2}}{V_0 V_{p2}}}{\frac{V_{p2}}{V_0 V_{p2}} + \frac{V_0}{V_0 V_{p2}}} \theta_0 , \frac{1}{1/V_0 + 1/V_{p2}} + V_{p3}\right)$$

- and could be expressed as

$$Y|x \sim N\left(\frac{\frac{1}{V_{p2}}}{\frac{1}{V_0} + \frac{1}{V_{p2}}} x + \frac{\frac{1}{V_0}}{\frac{1}{V_0} + \frac{1}{V_{p2}}} \theta_0 , \frac{1}{1/V_0 + 1/V_{p2}} + V_{p3}\right)$$

or equivalently

$$Y|x \sim N\left(\frac{\frac{x}{V_{p2}} + \frac{\theta_0}{V_0}}{\frac{1}{V_0} + \frac{1}{V_{p2}}}, \frac{1}{1/V_0 + 1/V_{p2}} + V_{p3}\right).$$

- The planned future phase 3 trial will have equal sample size allocation for the 2 groups and the total number of events in this phase 3 trial is *m*. We also assume that V_{p3} is known with value given by its estimate from (Parmar, 1998)

$$V_{p3} \approx \frac{4}{m}.$$

- The predictive posterior distribution, with V_{p3} replaced by its estimate, is of the form given in protocol Section 10.5.1 and as shown below

$$Y|x \sim N\left(\frac{\frac{x}{V_{p2}} + \frac{\theta_0}{V_0}}{\frac{1}{V_0} + \frac{1}{V_{p2}}}, \frac{1}{1/V_0 + 1/V_{p2}} + \frac{4}{m}\right).$$

- If we assume that the prior distribution is non-informative such that V_0 is a very large number relative to V_{p2},then the posterior predictive distribution (Gelman, 2013) is given could be reduced to

$$Y|x \approx N(x, V_{p2} + V_{p3}).$$

- Success in future phase 3 is defined as "observing a statistically significant one-sided 2.5% alpha-level log-rank test in a trial where sample size allocation in 2 groups is equal and the total number of events in the trial is *m*." The log-rank test statistic in the future phase 3 trial could be expressed as

$$Z_{p3} = \left(\log(\widehat{HR}_{p3}) * \sqrt{\frac{m}{4}}\right) \approx N(0,1).$$

- Under the null hypothesis of equality of hazard in phase 3, the one-sided 2.5% alpha-level log-rank test is statistically significant if

$$Z_{p3} < -1.96 \quad or\ equivalently, \quad y = \log(\widehat{HR}_{p3}) < -1.96 * \sqrt{\frac{4}{m}}.$$

- The probability of phase 3 success given phase 2 data is calculated using the predictive distribution of *Y* given *X*=*x*. This is the area under the posterior predictive distribution of *Y* given *X*=*x* in the region $Y < -1.96 * \sqrt{4/m}$, by virtue of the additional assumption that V_{p2} and V_{p3} are known. If $\Phi(\cdot)$ denotes the standard normal distribution function (i.e., $\Phi(-Z_\alpha) = \alpha$), then the predictive probability of phase 3 success, given phase 2 data, is calculated as

- $$\Phi\left(\frac{-1.96*\sqrt{\frac{4}{m}} - \left(\frac{\frac{x}{V_{p2}} + \frac{\theta_0}{V_0}}{\frac{1}{V_0} + \frac{1}{V_{p2}}}\right)}{\sqrt{\frac{1}{1/V_0 + 1/V_{p2}} + \frac{4}{m}}}\right).$$

- Assuming Non−informtaitve Prior, i.,e. V_0 is very large [relative to V_{p2}

$$Y|x \sim N\left(\left[\frac{V_0}{V_{p2} + V_{p0}}\right]x + \left[\frac{V_2}{V_2 + V_0}\right]\theta_0,\ \left(\frac{1}{\left[1/V_0\right] + \left[1/Vp_2\right]} + V_3\right)\right)$$

$$Y|x \sim N\left(\left[\frac{V_0}{V_{p2} + V_{p0}}\right]^{1} x + \left[\frac{V_2}{V_2 + V_0}\right]^{0}\theta_0,\ \left(\frac{1}{\left[1/V_0\right]^{0} + \left[1/Vp_2\right]} + V_3\right)\right)$$

$$\boldsymbol{Y|x \approx N\left(x,\ (V_{p2} + V_3)\right)}$$

  - Therefore, Phase 3 PoS given Phase 2 Data is:

$$P\left(Y < -1.96\sqrt{V_3} \mid x\right)$$

- This is area under Posterior Predictive Distribution of

$$Y|x \sim N\left(x, \left(V_{p2} + V_3\right)\right)$$

- Equivalently, this is the area under $N(0,1)$ to the left of

$$\frac{\left(-1.96\sqrt{V_3}\right) - x}{\sqrt{V_{p2} + V_3}}$$

$$V[log(sample\ HR)] = \left(\frac{1}{\#\ Events\ in\ Control}\right) + \left(\frac{1}{\#\ Events\ in\ Treatment}\right)$$

- Therefore:

$$V_{p2} = V[log(sample\ HR)\ from\ phase\ 2] \approx \frac{1}{n_c} + \frac{1}{n_t}$$

$$V_3 = V[log(sample\ HR)\ in\ phase\ 3] \approx \frac{4}{m}$$

note: m = total # events in a 2-arm study with equal allocation

- At final analysis, PoS is area under $N(0,1)$ to the left of

$$\frac{\left(-1.96\sqrt{V_3}\right) - x}{\sqrt{V_{p2} + V_3}}$$

or equivalently

$$\frac{\left(-1.96\sqrt{\frac{4}{m}}\right) - log(sample\ HR\ from\ platform\ trial)}{\sqrt{\frac{1}{n_c} + \frac{1}{n_t} + \frac{4}{m}}}$$

Model Checking & Diagnostics

- Before using the cox proportional hazard model, the proportional hazards assumption will be assessed using the following methods:
  - Kaplan-Meier plot by treatment arm
  - Plot of log(time) against log(-log(survival)) by treatment arm
  - Plot of Schoenfeld residuals for treatment
  - Evaluation of time-dependency of treatment effect by adding an interaction term of treatment and time in the Cox model. If the interaction term is significant ($p< 0.05$), it is considered that the proportional hazards assumption is violated.
- If one or more of the tests above demonstrates clear violation of the proportional hazards assumption, it is considered the proportional hazards assumption does not hold. Hazard ratio and corresponding 95% CI estimated from the Cox model will still be reported.

Model Results Presentation

- Cox proportional hazard model results will be summarised in tables accounting for the stratification factors. The median, 25th and 75th percentiles of OS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982) and presented in tables. In addition Kaplan Mier figures will presented to show the distribution of OS.

Sensitivity and Supportive Analyses

- If the proportional hazard assumption does not hold, additional analysis based on (Restricted Mean Survival Time) RMST may be explored.

- Sensitivity analyses will be conducted to evaluate time-dependency in the SoC arm. The exchangeability assumption will be examined by comparing overall survival between non-concurrent and concurrent SoC data, by using Cox's proportional hazard model with indicator in control data (0: nonconcurrent, 1: concurrent data) as a covariate. If there is a difference in OS between non-concurrent and concurrent SoC, this difference will be further investigated or examined. Sensitivity analysis will be conducted if there is evidence of a violation of the exchangeability assumption. An example of a sensitivity analysis is one where only the concurrent data will be included (i.e., no non-concurrent data are used) in evaluating the treatment effect of the experimental regimen at data analysis.
- A sensitivity analysis may be performed to adjust for the impact of COVID 19. The censoring rule as described below will be followed.
    a. Participants will be censored at the earliest date of,
        i. Treatment discontinuation related to COVID -19 and not associated with disease progression
        ii. Death due to COVID-19 infection and not associated with disease under study
    b. If none of the above events (i & ii) occurs and an event death occurs, the event will be based on the date of death due to any cause other than COVID-19 infection.
    c. Else if both a and b didn't occur then the participants will be censored at last known alive date, as per the primary analysis censoring rules.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

Part 1:

The secondary efficacy analyses for Part 1 will be based on safety population unless otherwise specified. The secondary endpoints in part 1 are, Overall Response Rate (ORR) and Disease Control Rate (DCR).

ORR is defined as the percentage of participants with a best overall confirmed CR or PR at any time as per RECIST1.1

DCR is defined as the percentage of participants with best overall confirmed complete response, partial response or stable disease at any time as per RECIST1.1

Summary measures for ORR and DCR will be provided as mentioned in Section 7.2.3.

Part 2:

The secondary efficacy analyses for Part 2 will be based on the ITT population, unless otherwise specified and all summaries and data listings will use treatment labels as specified in Section 5.1. The key secondary efficacy endpoint is Milestone Survival rate at 12 and 18 months. Other secondary endpoints are CR, PR,SD, PD, PFS, ORR, DOR, iCR, iPR, iUPD, iCPD, iSD, iPFS, iORR and iDOR which were used to evaluate anticancer activity.

- **Milestone Survival rate at 12 months** is defined as the percentage of people alive until 12 months after randomisation. It is the time from date of randomization to the date of death due to any cause during the period of 12 months. In the absence of confirmation of death during the period of 12 months, survival time will be censored at the last contact date. If the death date or date of last contact date is after 12 months then the censor date will be randomisation date + 12 months.

- **Milestone Survival rate at 18 months** is defined as the percentage of people alive until 18 months after randomisation. It is the time from date of randomization to the date of death due to any cause during the period of 18 months. In the absence of confirmation of death during the period of 18 months, survival time will be censored at the last contact date. If the death date or date of last contact date is after 18 months then the censor date will be randomisation date + 18 months.

The length of **Milestone Survival** will be calculated as

Milestone Survival = death date or last available date (during the period of 12 or 18 months) – date of randomization + 1

Subjects lacking data beyond date of randomisation will have their survival times censored at date of randomisation

The **Milestone Survival Rate** will be calculated as the (Kaplan Meir survival probabilities at time points 12 months/18 months) * 100.

For Anti-cancer activity Analyses, ITT population will be used unless otherwise specified. Anticancer activity will be evaluated based on clinical evidence and response criteria. The response data will be summarized by each treatment (iRECIST will be used for response endpoints and disease measurements for iORR, iDOR and iPFS; RECIST 1.1 guidelines will be used for response endpoints and disease measurements for ORR, DOR and PFS).

ORR, DCR, DOR and PFS as well as iORR, iDCR, iDOR and iPFS will be calculated and summarized.

ORR or iORR is defined as the percentage of participants with a best overall confirmed CR or PR at any time as per RECIST1.1/iRECIST.

DCR or iDCR is defined as the percentage of participants with best overall confirmed complete response, partial response or stable disease at any time as per RECIST1.1/iRECIST 1.1.

Best overall response (BOR) or **iBOR** will be derived on investigator assessments of oveall response at each visit recorded from the start of treatment until the criteria for progression are met (considering any requirement for confirmation when needed), or the date of initiation of new anti-cancer therapy (Note: This excludes palliative radiotherapy), or death date, whichever is earliest, as assessed by the investigator per RECIST 1.1 /iRECIST criteria.

For RECIST 1.1,

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

Responses of CR/PR that do not meet the requirements of confirmed CR/PR are still eligible to be considered SD if it has met the SD criteria.

For RECIST 1.1, to be assigned a status of SD, follow-up disease assessment(s) must have met the SD criteria at least once after the first dose at a minimum of 8 weeks (56 days) from baseline. If the minimum of 8 weeks (56 days) for SD is not met, the best overall response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum 8-week requirement the best response will be PD. Alternatively, subjects lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

For iRECIST, confirmatory disease assessment of PR or CR will be performed no less than 4 weeks (28 days) after the criteria for response are first met. In addition, a confirmatory disease assessment of PD will be performed no less than 4 weeks and up to 8 weeks later to confirm PD.

If NE (Not Evaluable) is recorded in between initial and confirmatory (i)CR or (i)PR or inbetween iUPD and iCPD then it can disregarded to obtain the Best Response

A SD in between an intial PR and confirmation PR can also be disregarded to obtain the Best Response of PR (see below table)

An iUPD between initial (i)CR/(i)PR and confirmed (i)CR/(i)PR can also be disregarded, as this can be considered to be a pseudo-progression

Assessment 1 (overall reponse)	Assessment 2 (overall reponse)	Assessment 3 (>= 4 weeks after) (overall reponse)	Assessment 4 (overall reponse)	Best Response
(i)CR	NE	(i)CR	-	(i)CR
(i)PR	NE	(i)PR	-	(i)PR
(i)PR	SD	(i)PR	-	(i)PR
(i)CR	NE	NE	(i)CR	(i)CR
(i)PR	NE	NE	(i)PR	(i)PR
iUPD	NE	NE	iCPD	iCPD
(i)CR	iUPD	(i)CR	-	(i)CR
(i)PR	iUPD	(i)PR	-	(i)PR
(i)PR	iUPD	iUPD	(i)PR	(i)PR

DOR or iDOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause among participants who achieve an overall response (i.e., unconfirmed or confirmed CR or PR). Censoring rules will follow those of the PFS analysis.

PFS or iPFS defined as time from the date of randomization to the date of disease progression per clinical or radiological assessment or death due to any cause, whichever occurs earlier. For the analysis of PFS, if the participant received subsequent anticancer therapy 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. Otherwise, if the participant does not have a documented date of event, PFS will be censored at the date of the last

adequate assessment.

The censoring rules for PFS and DOR are given below in Table 1:

Table 1 Censoring Rules for PFS and DOR

Situation	**Date of Event (Progression/Death due to any cause) or Censored[1]**	**Event (Progression/Death due to any cause)** **Or Censored**
Death due to any cause before first assessment (or Death at baseline or without any adequate assessments)	Date of death	Event
No adequate baseline assessments and the participant has not died due to any cause (if the participant has died due to any cause follow the rules for death indicted at the top of the table)	Randomization date	Censored
No post-baseline assessments and the participant has not died due to any cause (if the participant has died due to any cause follow the rules for death due to any cause indicated at the top of the table)	Randomization date	Censored
No adequate post-baseline assessment before start of new anticancer therapy	Randomization date	Censored
With post-baseline assessment but no progression (or death due to any cause)	Date of last 'adequate' assessment of response prior to any anti-cancer therapy	Censored
With adequate post-baseline assessment and new anticancer treatment started (prior to documented disease progression)[2] or death.	Date of last 'adequate' assessment of response (on or prior to starting anti-cancer therapy)	Censored
Death due to any cause or progression after missing two	Date of last 'adequate' assessment of response[3] (prior to missed assessments): If the disease assessment is every 6	Censored

Situation	**Date of Event (Progression/Death due to any cause) or Censored[1]**	**Event (Progression/Death due to any cause)** **Or Censored**
or more scheduled assessments	weeks, a window of 91 days ([12=6*2] weeks + 7 day window) will be used to determine whether there is extended time without adequate assessment. If the time difference between PD/death due to any cause and last adequate disease assessment is more than 91 days, PFS will be censored at the last adequate disease assessment prior to PD/death due to any cause. For scans conducted after 49 weeks, a window of 175 days ([24=12*2]weeks + 7 day window) will be used to determine whether there is extended time without adequate assessment.	
Progression documented[4]	Date of assessment of progression	Event[5]
Death due to any casue[4]	Date of death	Event

Notes:

[1] Event or censored are based on confirmed responses.
[2] 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).
[3] An adequate assessment is defined as an assessment where the response is (i)CR, (i)PR, (i)SD or any pseudo-progression (iUPD)
[4] If both progression and Death due to any cause are documented then take the earliest date
[5] If last response is iUPD and participant is still on treatment with no further response evaluation, then the participant will be censored at the last iUPD date for iPFS, else the participant will be considred for the event.

For iPFS, iRECIST requires the confirmation of progression and uses the terms unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD).

The progression event date (iPD date) to be used in the calculation of PFS per iRECIST should be the first date of documented iUPD provided that iCPD is confirmed at the next assessment.

If more than one assessment is recorded as iUPD then the final occurrence prior to iCPD will be used. The exception to the rule would be when consecutive iUPDs followed by iCPD, the first occurrence of iUPDs in a row prior to iCPD will be used. For example, if a participant has iUPD at time points 1 and 2 and iCPD at time point 3, then iPD date would be the date of time point 1. If iUPD occurs, but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date.

If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date will be used as iPD date in the following scenarios:

- Participant discontinues study intervention because the participant was judged not to be clinically stable
- Participant does not undergo further response assessments due to any reason (i.e., participant refusal, protocol non-compliance, or participant death)
- Next timepoint response of iUPD, and iCPD never occurs

7.2.2. Summary Measure

ORR

The number and percentage of participants with the BOR in the following response categories will be summarized: CR, PR,iCR,iPR. The corresponding exact 95% CI for ORR and iORR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response. A figure displaying maximum reduction in tumor size and listing of subject level responses will be generated.

DCR

The number and percentage of participants with the BOR in the following response categories will be summarized: CR, PR, SD, iCR,iPR, iSD. The corresponding exact 95% CI for DCR and iDCR will also be provided. Participants with unknown or missing responses will be treated as non-responders, i.e., these participants will be included in the denominator when calculating percentages of response.

DOR

The distribution of DOR will be summarized using the Kaplan-Meier method by treatment arm. The median, 25th and 75th percentiles of DOR will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982). Results from this will be descriptively summarised in tables and plotted, alogn with subject level listing of DOR.

PFS

The distribution of PFS for each treatment arm at will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of PFS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982). Results from this will be descriptively summarised in tables and plotted, along with subject level listing of PFS.

Milestone survival rate

The distribution of Milestone survival rate for each treatment arm at 12 months and 18 months will be estimated using the Kaplan-Meier method. The median, 25th and 75th percentiles of OS will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982). Results from this will be descriptively summarised in tables and plotted, along with subject level listing of milestone survival.

7.2.3. Population of Interest

The secondary efficacy analyses will be based on the ITT population, unless otherwise specified.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. Key secondary endpoints, such as PFS, DOR and milstone survival rate will be analysed (see Section 7.2.4.1). Response rates estimates will be reported with 95% exact CI in the summary tables.

7.2.4.1. Statistical Methodology Specification

Endpoint / Variables
• PFS, DoR
Model Specification
• Hazard ratio for PFS and DoR and corresponding 95% confidence interval will be estimated using the Cox's proportional hazard model stratified by the randomization factor(s) with treatment arm as the sole explanatory variable.
Model Checking & Diagnostics
The proportional hazards assumption will be assessed using the following methods: ○ Kaplan-Meier plot by treatment arm ○ Plot of log(time) against log(-log(survival)) by treatment arm

- Plot of Schoenfeld residuals for treatment
- Evaluation of time-dependency of treatment effect by adding an interaction term of treatment and time in the Cox model. If the interaction term is significant ($p< 0.05$), it is considered that the proportional hazards assumption is violated.

- If one or more of the tests above demonstrates clear violation of the proportional hazards assumption, it is considered the proportional hazards assumption does not hold. Hazard ratio and corresponding 95% CI estimated from the Cox model will still be reported.
- Additional analysis of PFS and DoR are based on RMST, which does not require the proportional hazard assumption may be conducted.

Text below describes RMST Option 1: Commonly used pre-specified time-point:

Minimum of last event time in treat and control

Minimum of last observed time in treat and control

Time of clinical interest, e.g., 2 yrs.

SAS macro for calculation is available at: http://bcb.dfci.harvard.edu/~huno/computer-program/rmst2_ver003.sas

Text below describes RMST Option 2: The time interval should be between "larger than the maximum of smallest event time" and "smaller than the minimum of largest follow up time". R code for calculation is available at: http://onlinelibrary.wiley.com/doi/10.1111/biom.12384/abstract

Model Results Presentation

Cox proportional hazard model results will be summarised in tables accounting for the stratification factors. The median, 25th and 75th percentiles of PFS/DoR will be estimated and corresponding 95% confidence intervals will be estimated using the Brookmeyer-Crowley method (Brookmeyer, 1982) and presented in tables. In addition Kaplan Mier figures will presented to show the distribution of PFS and DoR.

Sensitivity and Supportive Analyses

If the proportional hazard assumption does not hold additional analysis based on RMST may be explored.

Endpoint / Variables

- ORR and DCR

Model Specification

- ORR and DCR will be compared between treatment arms using Cochran's Mantel Haenszel test stratified by randomization factors. The exact 95% confidence interval for the difference will be calculated.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified.

8.1. Extent of Exposure

Extent of exposure to SOC and experimental arm will be summarized by Number of cycles, relative dose intensity and duration of exposure (see Section 12.6.2 for derivation details).

Relative dose intensity (RDI) is the percentage of the actual dose delivered relative to the intended dose. Relative dose intensity (RDI) is defined as (Actual cumulative dose delivered up to treatment discontinuation)/(Planned cumulative dose up to treatment discontinuation)*100. The planned cumulative dose is the total dose that would be delivered, if there were no modification to dose or schedule. An RDI of 100% indicates that the drug was administered at the dose planned per protocol, without delay or reductions.

Treatment compliance is defined as (Actual cumulative dose/Scheduled cumulative dose)*100. The scheduled dose accounts for any dose reductions, for example, if a participant had a dose reduction from 75 mg/m^2 to 60 mg/m^2, then the scheduled dose is 60 mg/m^2.
Summary statistics will be produced for extent of exposure.

Duration of Exposure in weeks is defined as (treatment stop date – treatment start date + 1) divided by 7.
For ITT Population, if subjects were randomized but did not receive any dose they will be counted as having zero duration of exposure. Duration of Study treatment will be plotted.

If the dose was not given at a particular visit , missed doses will be summarised and will include:

- number and percent of subjects with any missed doses. Each subject will only be counted once. The percentage will be based on “N”.
- total number of missed doses (events).
- number and percent of subjects with any missed doses by category. Number of missed doses will be categorized as 0, 1, 2, 3 or more, and Not Evaluable. Not evaluable row is for subjects who did not receive any drug in any succeeding time period after the first dose. Each subject will only be counted once. The number from each row will add up to N. The percentage will be based on “N”.
- number and percentage of missed doses (events) categorized by the reasons for missing a dose. Subject may be counted in multiple times in the same ‘reason’ row if the subject missed the dose multiple times for the same reason. Also, note that the same subject may be counted in multiple

reason rows, since they could have been missed a dose at different time points for different reasons. Therefore, the total number of events counted in different reasons must add up to the total number of missed doses (i.e. the number in the 2nd section of the table). The percentage will be based on the total number of missed doses (events).

Dose reductions will be summarised by treatment.The summary will include :

- number and percent of subjects with any reduction. Each subject will only be counted once. The percentage will be based on "N".
- total number of dose reductions (events).
- number and percent of subjects with any dose reduction by category. Number of dose reductions will be categorized as 0, 1, 2, 3 or more, and Not Evaluable. Not evaluable row is for subjects who did not receive any drug in any succeeding time period after the first dose. Each subject will only be counted once. The number from each row will add up to N. The percentage will be based on "N".
- number and percentage of dose reductions (events) categorized by the reasons. Subject may be counted in multiple times in the same 'reason' row if the subject had multiple dose reductions for the same reason. Also, note that the same subject may be counted in multiple reason rows, since their doses could have been reduced at different time points for different reasons. Therefore, the total number of events counted in different reasons must add up to the total number of dose reductions (i.e. the number in the 2nd section of the table). The percentage will be based on the total number of dose reductions (events).

Dose delays will be summarized by treatment and this will include:

- number and percent of subjects with any delay. Each subject will only be counted once. The percentage will be based on "N".
- total number of delays (events).
- number and percent of subjects with any dose delays by category. Number of dose delays will be categorized as 0, 1, 2, 3 or more, and Not Evaluable. Not evaluable row is for subjects who did not receive any drug in any succeeding time period after the first dose. Each subject will only be counted once. The number from each row will add up to N. The percentage will be based on "N".
- number and percent of dose delays (events) categorized by duration in days (e.g. 1-7, >=8 etc.). The percentages will be based on the total number of dose delays (i.e. the number from the 2nd section of the table). Subject may be counted in multiple times in the same 'duration' row if the subject had multiple dose delays for the same duration. Also, note that the same subject may be counted in multiple duration rows, since their doses could have been delayed at different time points for different lengths of time.
- number and percentage of dose delays (events) categorized by the reasons. Subject may be counted in multiple times in the same 'reason' row if the subject had multiple dose delays for the same reason. Also, note that the same subject may be counted in multiple reason rows, since their doses could have been delayed at different time points for different reasons.

Therefore, the total number of events counted in different reasons must add up to the total number of dose delays (i.e. the number in the 2nd section of the table). The percentage will be based on the total number of dose delays (events).

Dose delay duration will be calculated as [start date of delayed dose - (start date of previous dose + 21)]

If the infusions were stopped early and not completed it will be collected as incomplete infusions. Summary of Incomplete Infusion (by treatment) will include:

- number and percent of subjects with any incomplete infusion. Each subject will only be counted once. The percentage will be based on "N".
- total number of incomplete infusions (events).
- number and percent of subjects with any incomplete infusion by category. Number of incomplete infusion will be categorized as 0, 1, 2, 3 or more. Each subject will only be counted once. The number from each row will add up to N. The percentage will be based on "N".
- number and percentage of incomplete infusions (events) categorized by the reasons for stopping an infusion. Subject may be counted in multiple times in the same 'reason' row if the subject had incomplete infusion multiple times for the same reason. Also, note that the same subject may be counted in multiple reason rows, since they could have had incomplete infusions at different time points for different reasons. Therefore, the total number of events counted in different reasons must add up to the total number of incomplete infusions (i.e. the number in the 2nd section of the table). The percentage will be based on the total number of incomplete infusion (events).

If the infusions were intermittently interrupted but ultimately the infusion was completed it will be collected as infusion interruption. Summary of Infusion Interruptions (by treatment) will include:

- number and percent of subjects with any infusion interruptions. Each subject will only be counted once. The percentage will be based on "N".
- total number of infusion interruptions (events).
- number and percent of subjects with an infusion interruption by category. Number of infusion interruptions will be categorized as 0, 1, 2, 3 or more. Each subject will only be counted once. The number from each row will add up to N. The percentage will be based on "N".
- number and percentage of infusion interruptions (events) categorized by the reasons for interruption. Subject may be counted in multiple times in the same 'reason' row if the subject has infusion interruptions multiple times for the same reason. Also, note that the same subject may be counted in multiple reason rows, since they could have had infusion interruptions at different time points for different reasons. Therefore, the total number of events counted in different reasons must add up to the total number of infusion interruptions (i.e. the number in the 2nd section of

the table). The percentage will be based on the total number of infusion interruptions (events).

All dose reductions, infusion interruptions and incomplete infusions, and dose delays will be listed separately by treatment.

8.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious adverse events (SAEs) and other significant AEs will be based on GSK Core Data Standards. Details on treatment emergent AEs are provided in Section 12.4.2. Dose modifications, dose interruptions, dose reduction dose delays will also be summarized and listed according to GSK Oncology Data Standards. The details of the planned displays are provided in Appendix 10: List of Data Displays.

AEs will be coded using the standard MedDRA v.21.1. and grouped by system organ class. AEs will be graded by the investigator according to the NCI-CTCAE (version 5.0).

Summary of all Adverse Events and Drug related Adverse events by System Organ Class and Preferred Term and Maximum Grade will be reported. Summary of Grade 3-5 AEs and drug related Grade 3-5 AEs that occurred in ≥5% of participants will be provided by Overall frequency.

A summary of non-serious AEs that occurred in strictly 5% of the participants or above will be provided (no rounding for the percentage will be used in terms of 5% threshold, e.g. events with 4.9% incidence rate should not be included in this table).

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

- **Preferred term row**: Participants experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each participant with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.
- Summary of non-serious drug related adverse events by overall frequency by PT will be produced.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced. Listing of relationship of adverse event System Organ Class (SOC), Preferred term (PT) and verbatim text will be produced.

AEs with missing date of onset will be considered treatment-emergent.

8.3. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. 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 details of the planned displays are provided in Appendix 10: List of Data Displays.

AESI are currently defined as events of potential immunologic etiology (irAEs) (however this may change over time due to emerging data and analysies). Such events recently reported after treatment with other immune modulatory therapy include but not limited to:

AE of Special Interest	AE of Special Interest - Sub class	Preferred Term (MedDRA Version 21.1)	System Organ Class	MedDRA Code
The following is the synonyms of AEs of special interest will be combined under the PT as shown below. Note the AE of special interest groups may overlap to each other, i.e., one PT may be accounted for multiple AE of special interest groups.				
Potential Immune-Mediated Disorders	**Pneumonitis**	Pneumonitis	Respiratory, thoracic and mediastinal disorders	10035742
		Dyspnoea	Respiratory, thoracic and mediastinal disorders	10013968
		Cough	Respiratory, thoracic and mediastinal disorders	10011224
		Dyspnoea exertional	Respiratory, thoracic and mediastinal disorders	10013971
		Rales	Respiratory, thoracic and mediastinal disorders	10037833
		Upper-airway cough syndrome	Respiratory, thoracic and mediastinal disorders	10070488
		Wheezing	Respiratory, thoracic and mediastinal disorders	10047924

AE of Special Interest	AE of Special Interest - Sub class	Preferred Term (MedDRA Version 21.1)	System Organ Class	MedDRA Code
		Pneumonia	Infections and infestations	10035664
		Pneumothorax	Respiratory, thoracic and mediastinal disorders	10035759
		Respiratory distress	Respiratory, thoracic and mediastinal disorders	10038687
		Hypoxia	Respiratory, thoracic and mediastinal disorders	10021143
	Myocarditis	Myocarditis		
		Troponin Increased		
		Cardiac Ischemia		
		Myocardial Infarction		
	Colitis	Colitis	Gastrointestinal disorders	10009887
		Diarrhea	Gastrointestinal disorders	10012735
	Hepatitis	Alanine aminotransferase increased	Investigations	10001551
		Aspartate aminotransferase increased	Investigations	10003481
		Blood alkaline phosphatase increased	Investigations	10059570
		Blood bilirubin increased	Investigations	10005364
		Hepatocellular injury	Hepatobiliary disorders	10019837
		Immnue-mediated hepatitis	Hepatobiliary disorders	10078962
		Hepatitis	Hepatobiliary disorders	10019717

AE of Special Interest	AE of Special Interest - Sub class	Preferred Term (MedDRA Version 21.1)	System Organ Class	MedDRA Code
		Hepatic function abnormal	Hepatobiliary disorders	10019670
		Transaminases increased	Investigations	10054889
		Gamma-glutamyltransferase increased	Investigations	10017693
	Endocrinopathies	Hypophysitis	Endocrine disorders	10062767
		Hypopituitarism	Endocrine disorders	10021067
		Hypothyroidism	Endocrine disorders	10021114
		Hyperthyroidism	Endocrine disorders	10020850
		Hyperglycaemia	Metabolic and nutrition disorders	10020635
	Nephritis and Renal Function	Renal impairment	Renal and urinary disorders	10062237
		Acute kidney injury	Renal and urinary disorders	10069339
		Blood creatinine increased	Investigations	10005483
		Proteinurea	Renal and urinary disorders	10037032
		Nephritis	Renal and urinary disorders	10029117
		Pyelonephritis acute	Infections and infestations	10037597
		Urinary retention	Renal and urinary disorders	10046555
		Uninary incontinence	Renal and urinary disorders	10046543
		Micturition urgency	Renal and urinary disorders	10027566
	Skin Adverse Reactions	Rash	Skin and subcutaneous tissue disorders	10037844

AE of Special Interest	AE of Special Interest - Sub class	Preferred Term (MedDRA Version 21.1)	System Organ Class	MedDRA Code
		Rash maculo-papular	Skin and subcutaneous tissue disorders	10037868
		Rash Papular	Skin and subcutaneous tissue disorders	10037876
		Pruritus	Skin and subcutaneous tissue disorders	10037087
		Erythema	Skin and subcutaneous tissue disorders	10015150
		Dermatitis	Skin and subcutaneous tissue disorders	10012431
		Palmar-plantar erythrodysaesthesia syndrome	Skin and subcutaneous tissue disorders	10033553
		Skin infection	Infections and infestations	10040872
		Skin ulcer	Skin and subcutaneous tissue disorders	10040943
		Urticaria	Skin and subcutaneous tissue disorders	10046735
		Vulvovaginal pruritus	Reproductive system and breast disorders	10056530
		Cellulitis	Infections and infestations	10007882
		Eye Pruritus	Eye disorders	10052140
		Skin fissures	Skin and subcutaneous tissue disorders	10040849
	Other Immune-Mediated Adverse Events	Pancreatitis	Gastrointestinal disorders	10033645
		Lipase increased	Investigations	10024574
		Amylase increased	Investigations	10002016

AE of Special Interest	AE of Special Interest - Sub class	Preferred Term (MedDRA Version 21.1)	System Organ Class	MedDRA Code
		Arthritis	Musculoskeletal and connective tissue disorders	10003246
Infusion-Related Reactions		Chills	General disorders and administration site conditions	10008531
		Wheezing	Respiratory, thoracic and mediastinal disorders	10047924
		Pruritus	Skin and subcutaneous tissue disorders	10037087
		Flushing	Vascular disorders	10016825
		Rash	Skin and subcutaneous tissue disorders	10037844
		Hypotension	Vascular disorders	10021097
		Infusion related reaction	Injury, poisoning and procedural complications	10051792
		Orthostatic hypotension	Vascular disorders	10031127

Summaries of the number and percentage of subjects with AESI will be provided for each type of event separately by preferred term and maximum grade.

Summary of Onset and Duration of the First Occurrence of AESI will also be produced.

8.4. Deaths and Serious Adverse Events

All deaths will be summarised based on the number and percentage of participants. This summary will classify participants by time of death relative to the last dose of medication (>30 days or ≤30 days) and primary cause of death (disease under study, SAE related to study treatment, or other). A supportive listing will be generated to provide participant-specific details on participants who died.

All SAEs will be tabulated based on the number and percentage of participants who experienced the event. The summary table will be displayed in descending order of total

incidence by SOC and PT.Summary of Drug related SAE, fatal SAE, drug-related fatal SAE will also be produced

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.

A listing of reasons for considering an SAE will be provided.

8.5. 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 participant level details for those participants:

- AEs Leading to Discontinuation of Study Treatment
- AEs Leading to Withdrawal from the Study
- AEs Leading to Dose Interruptions
- AEs Leadings to Dose Reductions
- AEs Leading to Missed Doses

An AE leading to dose modification is an AE for which the action with respect to dosing is recorded as reduction or interruption of dose. AEs that lead to both a dose modification and a discontinuation of study treatment will only appear in the AEs leading to discontinuation of study treatment summary.

8.6. 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 subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

8.7. Clinical Laboratory Analyses

Laboratory grades will be reported using the Common Terminology Criteria for Adverse Events (CTCAE v5.0). The assessment of laboratory toxicities will examine the following laboratory tests performed by local laboratories:

Laboratory Assessments	**Parameters**			
Hematology	RBC Indices	WBC count with Differential		Platelets
	Hemoglobin	Neutrophils		
	Hematocrit	Lymphocytes		
	RBC count	Monocytes		
		Eosinophils		
		Basophils		
Clinical Chemistry	BUN[a]	Potassium	Bilirubin	AST (SGOT)
	Creatinine[b]	Sodium	Total protein	ALT (SGPT)
	Glucose	Calcium	Albumin	Alkaline phosphatase
	LDH			
Coagulation	INR or PT			
	PTT/aPTT			
Cardiac Function	Troponin I or Troponin T			
Thyroid Function	Thyroid stimulating hormone Free T4 Free T3 (when clinically indicated)			
Routine Urinalysis	Specific gravity pH, glucose, protein, blood and ketones by dipstick (Note: routine urinalysis by method other than dipstick is acceptable, in accordance with local practice).			
Other Screening Tests	Hepatitis B surface antigen (HBsAg) Hepatitis C (Hep C antibody)[c] Serum β-hCG Pregnancy test (for women of child bearing potential)			

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; HBsAg = Hepatitis B surface antigen; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; T3 = triiodothyronine; T4 = thyroxine; WBC = white blood cells; INR = International Normalized Ratio; PT = Prothrombin Time; aPTT = Activated Partial Thromboplastin Time

a. Required if local laboratory testing is available
b. Creatinine clearance is also required to be calculated using the formula provided in Appendix 9 of the protocol.
c. Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C RNA test is obtained. Hepatitis C RNA Test is optional with negative Hepatitis C antibody test.
d. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all participants. Any participant receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study

Change from baseline by scheduled visits will be summarised using mean, median, standard deviation, minimum, and maximum.

Summaries of worst case grade increase from baseline grade will be provided for all the lab tests that are gradable by CTCAE v5.0. These summaries will display the number and percentage of participants 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. In addition, the summary will include grade

increase from baseline by scheduled visits. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled bi-direction, e.g. sodium will be summarized as hyponatremia and hypernatremia.
For lab tests that are not gradable by CTCAE v5.0, 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 at each scheduled visit as well as for the worst case post-baseline. . If a participant has a "Decrease to low" and an "Increase to high" during the same time interval, then the participant is counted in both the "Decrease to Low" category and the "Increase to High" category. In addition, the summary will include worst case changes from baseline with respect to normal range by scheduled visits.

Separate summary tables for hematology and chemistry laboratory tests will be produced.

Listing of Laboratory values of Potential Clinical Importance and listing of all laboratory values for any value of potential clinical importance will be produced

A separate listing of laboratory data with character values will also be provided. Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of participants with non-missing value at each visit.

Urinalysis Results will be summarised. Worst-case Urinalysis Results Post-Baseline Relative to Baseline will be summarised

A character lab value starting with '<X' or '>X' will be displayed in listings but will not be imputed with a numeric value thus will not be included for summaries.

8.8. Liver Function Analyses

Summaries of hepatobiliary laboratory abnormalities will be produced

Possible Hy's law cases are defined as any elevated (ALT ≥3×ULN and overall 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 subjects receiving anticoagulants.

8.9. Other Safety Analyses

The analyses of non-laboratory safety test results including vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 10: List of Data Displays.

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.

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 supporting listing will also be provided.

Vital Signs

The following summaries will be provided for vital signs data:

- Summary of Changes in Heart Rate from Baseline
- Summary of Increases in Blood Pressure from Baseline
- Summary of Changes in Temperature from Baseline

The following listing will also be produced

- Listing of Vital Signs with Values of Potential Clinical Importance

The oncology standard categories for Heart Rate in bpm is:

- Heart Rate in bpm: 'Decrease to <60', 'Increase to >100'

The oncology standard categories for Systolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (140-159)'
- 'Increase to Grade 3 (>=160)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<120), Grade 1 (120-139), Grade 2 (140-159), Grade 3 (>=160).

The oncology standard categories for Diastolic Blood Pressure in mmHg are:

- 'Any Grade Increase'
- 'Increase to Grade 2 (90-99)'
- 'Increase to Grade 3 (>=100)'

Note: 'Any Grade Increase' will be footnoted as Grade 0 (<80), Grade 1 (80-89), Grade 2 (90-99), Grade 3 (>=100).

The oncology standard category 'Decrease to < 90' will be used for the Summary of decreases in Systolic Blood Pressure from Baseline.

The oncology standard categories of clinical concern for Temperature are:

- Temperature in C: 'Decrease to <=35', 'Increase to >= 38'

COVID-19 Assessments

Confirmed, probable and suspected COVID 19 cases will be summarized and listed. Visits impacted by COVID-19 Pandemic will be summarized. Number of subjects with missed visits, site visits with one or more assessment missed, remote visit with no assessments missed and remote visit with one or more assessments missed will be summarized with primary reason for the impact.

Dose Limiting Toxicity

For part 1 of the study, a listing of adverse events recorded as dose-limiting toxicities during the determinative period will be provided. Additionally, a summary of the number of patients experiencing DLTs will be provided.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

There are no primary pharmacokinetic analyses for this study.

9.2. Secondary Pharmacokinetic Analyses

9.2.1. Endpoint / Variables

9.2.1.1. Drug Concentration Measures

Details are included in Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Standards for Pharmacokinetic)

9.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters for GSK3359609 and Docetaxel will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of Phoenix WinNonlin.

All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the GSK3359609 and Docetaxel concentration-time data, as data permits.

In addition to non-compartmental PK analysis, a preliminary population PK model developed from Phase I study 204691 may also be used to overlay observations from this study on PK model predictions (visual predictive check plots), and covariates may be explored to understand the variability in Cmax and Cmin parameters. To further support interpretation of PK data collected on 205801, PK information may be pooled with data from other trials and indications, including the phase I first-time-in-human (FTIH) study to develop and evaluate a basic structural PK model. This may be reported separately.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time 0 to the time of last quantifiable concentration will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
Cmax	Maximum observed plasma concentration, determined directly from the concentration-time data.
Cmin	Minimum observed concentration
Ctau	Pre-dose (trough) drug concentration, where tau is the end of the dosing interval

NOTES:

- Additional parameters may be included as required.

9.2.2. Summary Measure

Plasma Concentration data will be summarised separately for GSK3359609 and Docetaxel. Corresponding listing of the plasma concentration values will also be produced. Individual plasma concentration-time plots by subject, mean concentration-

time plots and median concentration time plots will be produced for GSK3359609 and Docetaxel separately.
For each of these parameters for GSK3359609 and Docetaxel separately, the following summary statistics will be calculated for each treatment and presented separately: median, minimum, maximum, arithmetic mean, 95% confidence interval for the arithmetic mean, standard deviation, coefficient of variation (%CV = 100*(sqrt (exp(SD^2) - 1))) [NOTE: SD = SD of natural log (log_e) transformed data]), geometric mean, 95% confidence interval for the geometric mean and standard deviation of natural logarithmically transformed data.

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.

All derived PK parameters will be listed.

9.2.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

9.2.4. Strategy for Intercurrent (Post-Randomization) Events

Not Applicable

10. SECONDARY ANALYSES

10.1. Immunogenicity Analyses

Serum samples will be collected and tested for the presence of antibodies that bind to GSK3359609 (ICOS agonist). These samples may also be tested for presence of antibodies that bind to Chinese Hamster Ovary (CHO) host cell proteins such as phospholipase B- like (PLBL2).

The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SRM.

Immunogenicity testing will occur in dosed subjects then analyzed, summarized descriptively and/or presented graphically.

Immunogenicity information will be listed by subject and a summary of the number of subjects that are negative and positive for the presence of the antibodies will be provided at each timepoint and overall for the subject. Drug tolerance of the assays will be taken into account in categorizing results at each timepoint as positive, negative, or inconclusive. A positive result at any timepoint means that the subject's overall category is positive.

10.2. Patient Reported Outcomes

Patient reported outcomes will be summarized in part 2 of the study.

10.2.1. Endpoint / Variables

CCI

[redacted]

10.2.2. Population of Interest

The PRO analyses will be based on the ITT population, unless otherwise specified.

10.2.3. Statistical Measures

10.2.3.1. Summary Measure

CCI

[redacted]

CCI

CCI


CCI

11. REFERENCES

CCI [redacted]

CCI [redacted]

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. New England Journal of Medicine. 2015;373(17):1627-39.

Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015; 373:123-35.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics, 1982; 38:29-41.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guidelines (version 1.1). Eur J Cancer. 2009; 45:228-47.

CCI [redacted]

Gelman A, Carlin J, Stern H, et al. Bayesian Data Analysis. Third Edition. Boca Raton: CRC Press; 2013, page 41.

GlaxoSmiteKline Document Number 2017N337080_02: A Phase II, Randomized, Open-label Platform Trial Utilizing a Master Protocol to Study Novel Regimens Versus Standard of Care Treatment in NSCLC Participants.

Herbst RS, Baas P, Kim D-W, Felip E, Perez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small cell lung cancer (KEYNOTE-010): a randomised controlled trial. The Lancet. 2016;387(10027):1540-50.

Parmar M, Torri V, Stewart L. Extracting Summary Statistics to Perform Meta-Analysis of the Published Literature for Survival Endpoints. Statistics in Medicine. 1998; 17:2815-2834.

Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology. 2017 Mar 1;18(3):e143-e152. https://doi.org/10.1016/S1470-2045(17)30074-8

Zhao L, Claggett B, Tian L, et al. On the restricted mean survival time curve in survival analysis. Biometrics. 2016; 72:215-221.Appendices

12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

There is no planned per protocol analysis for this study.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

The Schedules of Activities can be found in the corresponding substudy appendix in Section 12.1

12.3. Appendix 3: Assessment Windows

The visit assigned to the assessment as entered in the CRF (nominal visit) will be used for reporting.

12.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

12.4.1. Study Phases

Adverse events, serious adverse events, death and other safety domains will be assigned to the study phases defined below. Partial dates will be imputed into full dates, if applicable, for slotting data to the appropriate categories below. Flag variables (time in relation to study phase) indicating the study time periods will be added to the ADaM variable APHASE, and the treatment emergent AE flag will be created to ADAE variable TRTEMFL.

Assessments and events will be classified according to the time of occurrence relative to Study Treatment Start Date.

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date + 30 days
Post-Treatment	Date > Study Treatment Stop Date + 30 days

For parameters where time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Study Phase	Definition
Pre-Treatment	Date < Study Treatment Start Date
On-Treatment	Study Treatment Start Date ≤ Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

12.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to study treatment start date
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

12.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition

Treatment Emergent	**Non-serious AEs**
	In general, all AEs with a start date after treatment are considered emergent regardless of AE start date is before or after treatment stop date.
	
	• If AE onset date is on or after treatment start date & on or before treatment stop date + 30 days
	  ○ Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 days
	  ○ AE Start Date is missing
	Serious AE/AESI
	  ○ If AE onset date is on or after treatment start date & on or before treatment stop date + 30 days Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 30 days
	  ○ AE Start Date is missing
	Missing AE Start Date will be imputed following rules in Section 12.7.2.1 for determining Treatment Emergent AEs.

NOTES:

- [If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.]
- If the study treatment stop date is missing, then the AE will be On-Treatment.
- Time of study treatment dosing and start[/stop] time of AEs should be considered, if collected.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: US1SALX00259
HARP Compound	: Compound: GSK3359609, study: mid205801 Each IDMC interim and SAC relevant to eah substudy will be reported under mid205801 with a unique reporting effort.
Analysis Datasets	
• Analysis datasets will be created according to SDTM IG Version 3.2 & ADaM IG Version 1.1.	
Generation of RTF Files	
• RTF files will be generated for final SAC per substudy	

12.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings
• All data displays (Tables, Figures & Listings) will use the term “Subject” which reflects CDISC and GSK Data Display Standards terminology

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP’s) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP’s.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  o Unscheduled or unplanned readings will be presented within the subject’s listings.

Unscheduled Visits
• All unscheduled visits will be included in listings. • Unscheduled visits will not be included in summary tables and/or figures, except for worst case summary tables and/or figures.

Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

12.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not Applicable.
NONMEM/PK/PD File	Not applicable.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to GUI_51487

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time windowthe value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day for Safety and PK
• Calculated as the number of days from First Dose Date: ○ Ref Date = Missing → Study Day = Missing ○ Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date ○ Ref Date ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1
Study Day for ITT
• Calculated as the number of days from Randomization Date: ○ Ref Date = Missing → Study Day = Missing ○ Ref Date < Randomization Date → Study Day = Ref Date – Randomization Date ○ Ref Date ≥Randomization Date → Study Day = Ref Date – Randomization Date + 1
Change from Baseline
• Change from Baseline = Post-Baseline Visit Value – Baseline • % Change from Baseline= 100 x (Post-Baseline Visit Value – Baseline) / Baseline • Maximum Increase/Decrease from Baseline = maximum (Increase/Decrease from Baseline) • If either the Baseline or Post-Baseline Visit Value is missing, Change from Baseline and % Change from Baseline is set to missing
Date of Response
• For post-baseline disease assessments, the date of response (PR or better) is assigned to the latest date of disease assessments; for other response categories (SD [or Non-CR/Non-PD], NE, PD), the date of response is assigned to the earliest date of disease assessments.
Date of New Anti-Cancer Therapy
• Derived as the earliest date of new anti-cancer therapy, radiotherapy (where applicable) or surgical procedure (where applicable) • Missing or partial dates will be imputed for derivation of new anti-cancer therapy following rules specified in Section 12.7.2.1.
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 • For time to event (TTE) durations such as PFS

- To report 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)))

These algorithms 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.

12.6.2. Study Population

Demography

Age

- Age calculation will be based on Screening Date as the reference Date
- Birth date will be imputed as follows:

  Any subject with a missing day will have this imputed as day '15'.

  Any subject with a missing date and month will have this imputed as '30JUN'.

Extent of Exposure

- The cumulative dose will be based on the formula:

  Cumulative Dose = Sum of (the actual dose administered during each infusion)
- The relative dose intensity (%) is the infusion dose intensity divided by planned dose per week.

  Relative Dose Intensity = (Cumulative Dose /Planned Dose)*100

Actual Treatment

- Participant's actual treatment will be derived from exposure data. If a participant's actual treatment is the same as assigned treatment, actual treatment is the assigned treatment; if a participant received treatment different from assigned treatment for the entire duration of treatment, actual treatment is different from assigned treatment.

Time since Initial Diagnosis

- Calculated as the number of [Days] from the Date of Initial Diagnosis:
  - First Dose Date = Missing → Elapse Time = Missing
  - Date of Initial Diagnosis = Completely/partially Missing → Elapse Time = Missing
  - Otherwise → Elapse Time = First Dose Date – Date of Initial Diagnosis + 1

12.6.3. Safety

Adverse Events
AE'S OF Special Interest
Refer to Section 8.2
Duration of AE
• Calculated as the number of [days] from AE Start Date to AE Stop Date: ○ AE Start Date = Missing → Elapse Time = Missing ○ AE Stop Date = Missing → Elapse Time = Missing ○ Otherwise → Elapsed Time = AE Stop Date – AE Start Date + 1

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. • Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 • Example 2: 1 Significant Digit = '> x' becomes x + 0.1 • Example 3: 0 Significant Digits = '< x' becomes x – 1

12.6.4. Patient Reported Outcomes (PRO)

CCI

[redacted]

CCI

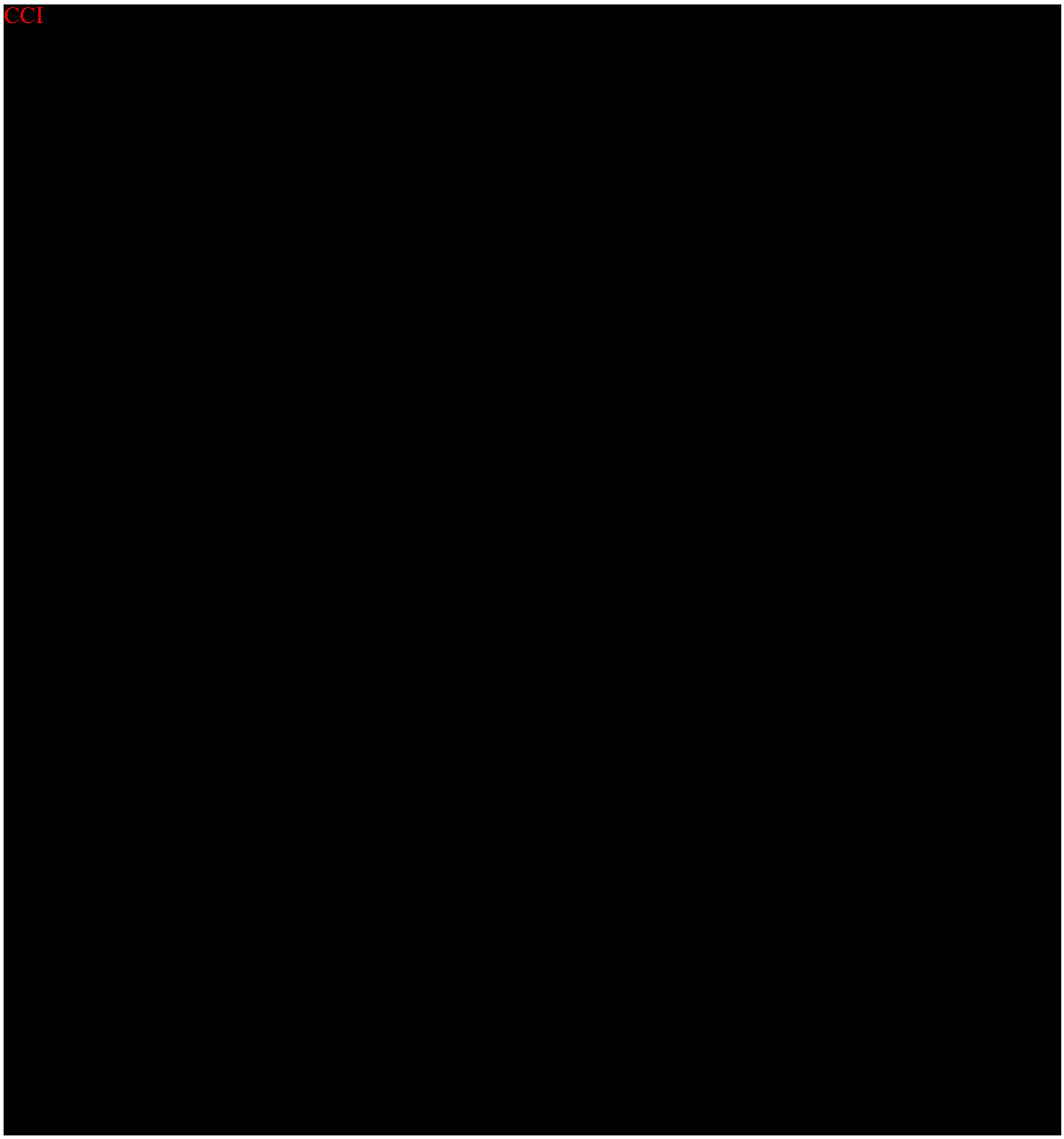
[redacted]

CCI

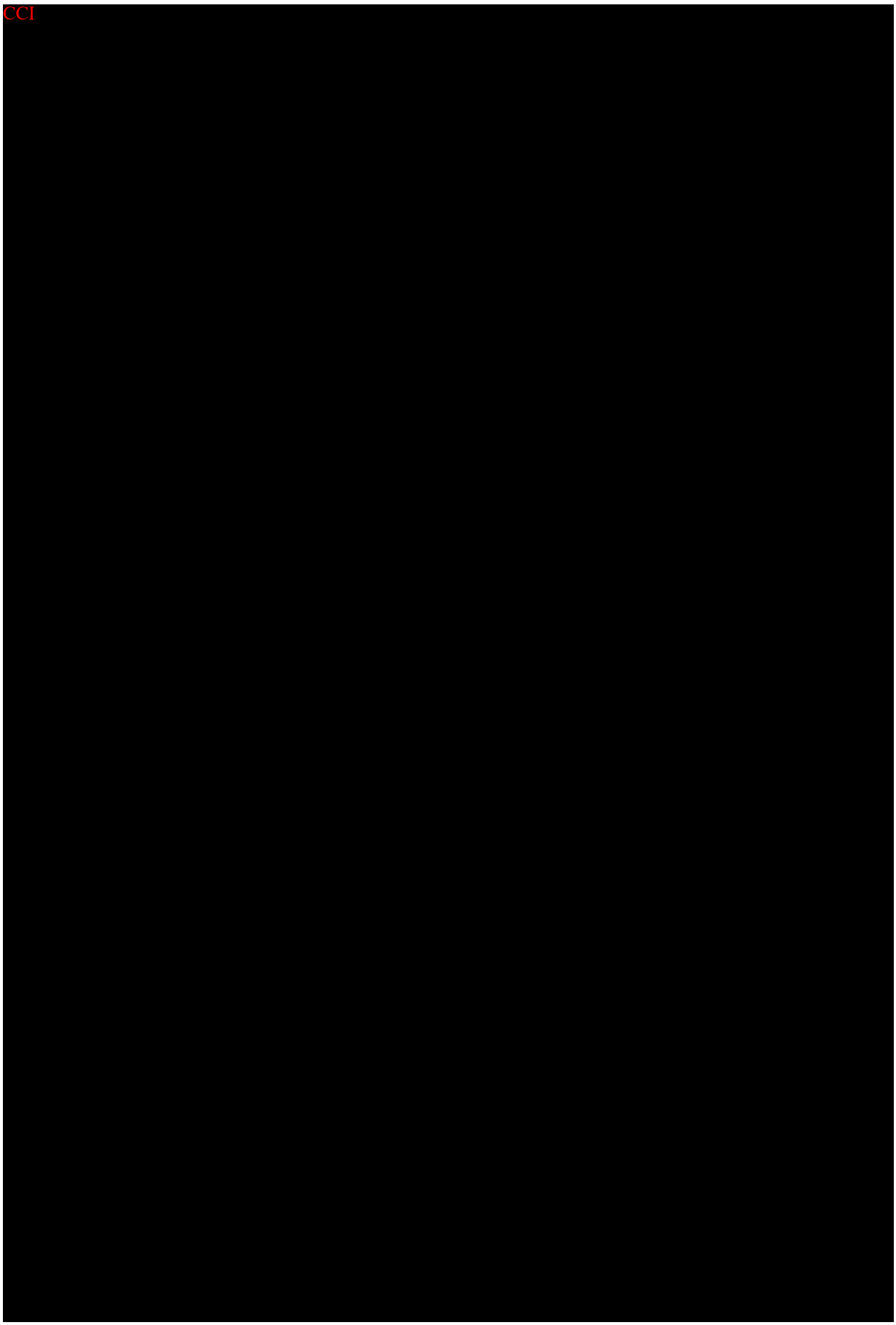
[redacted]

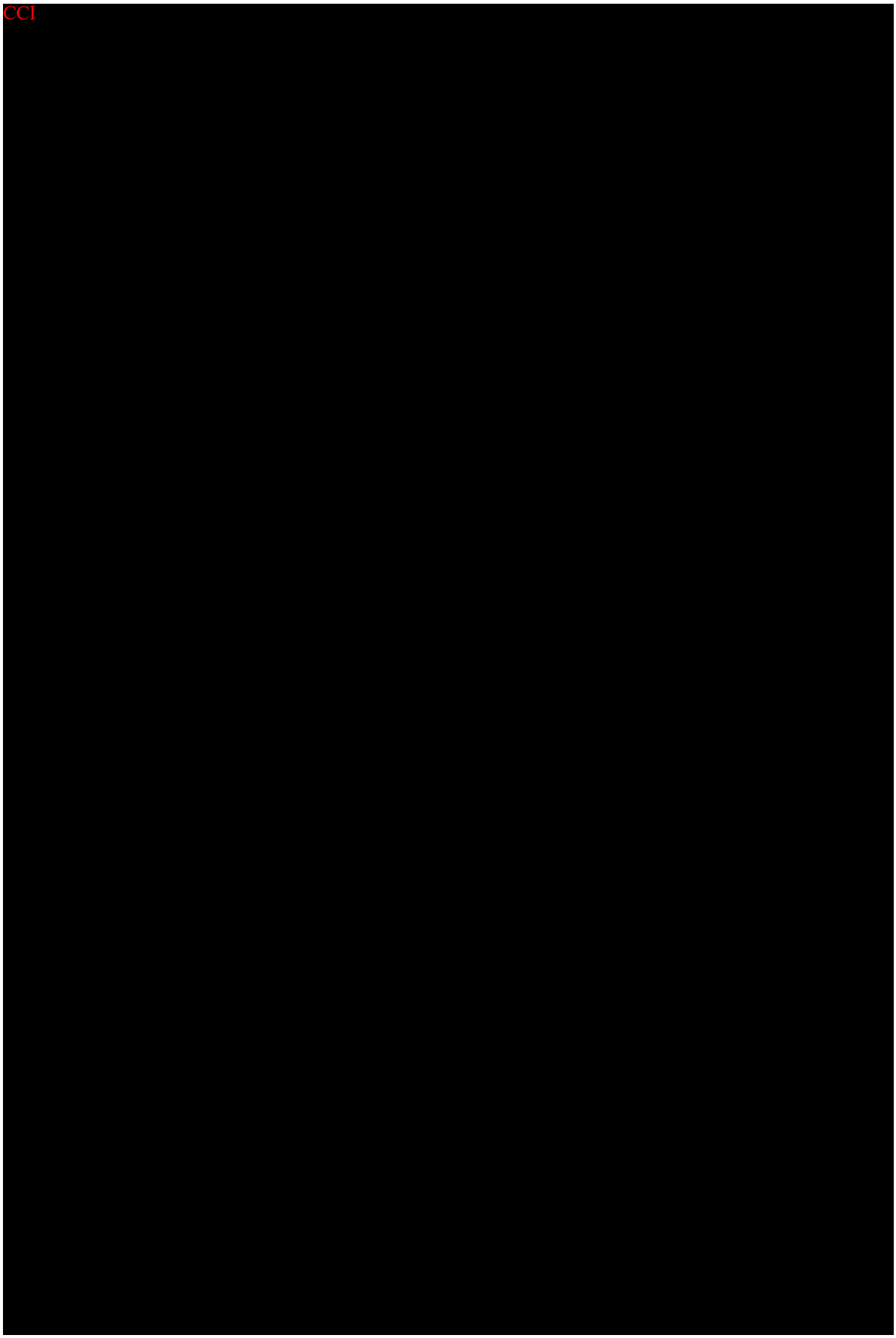
CCI

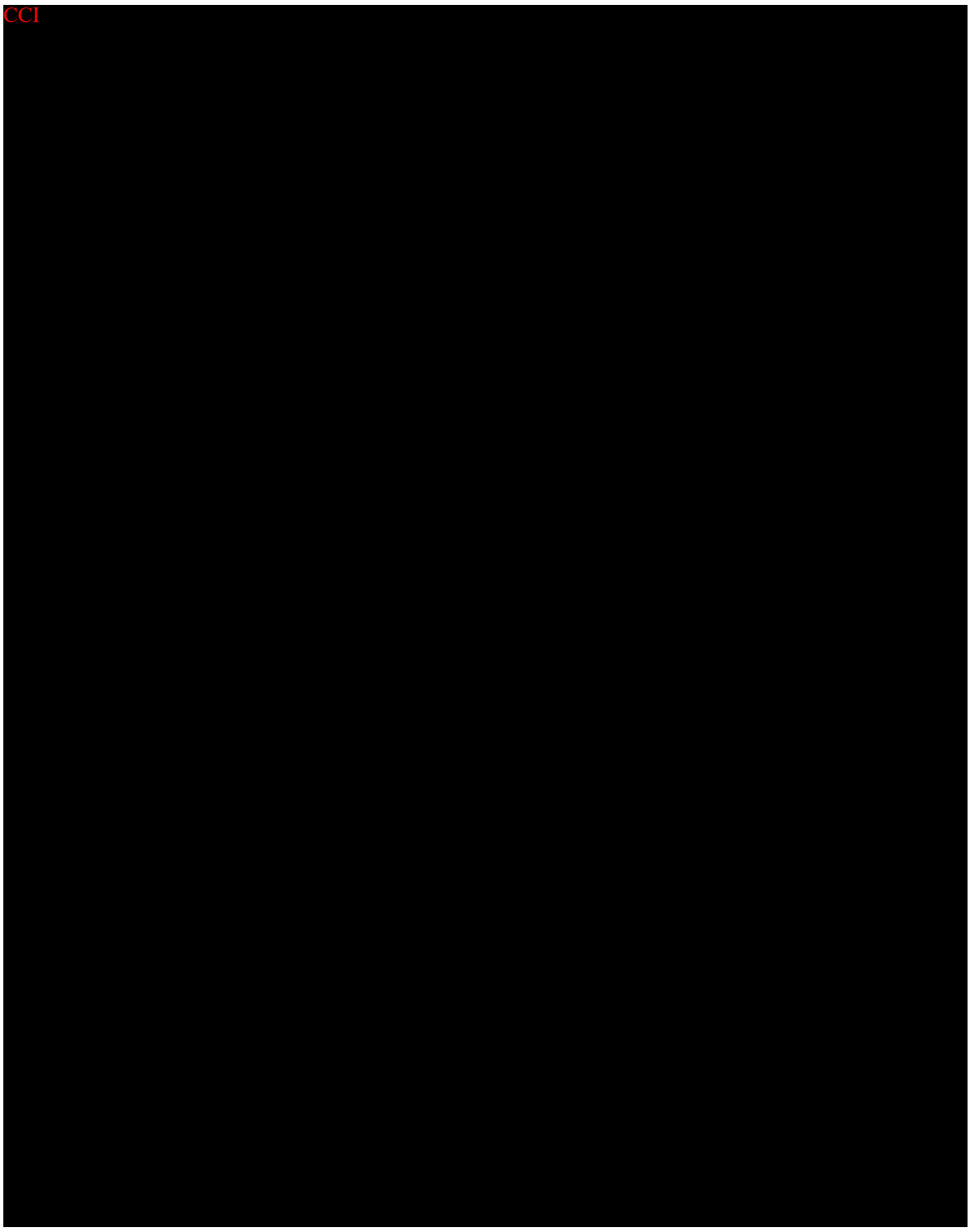
CCI



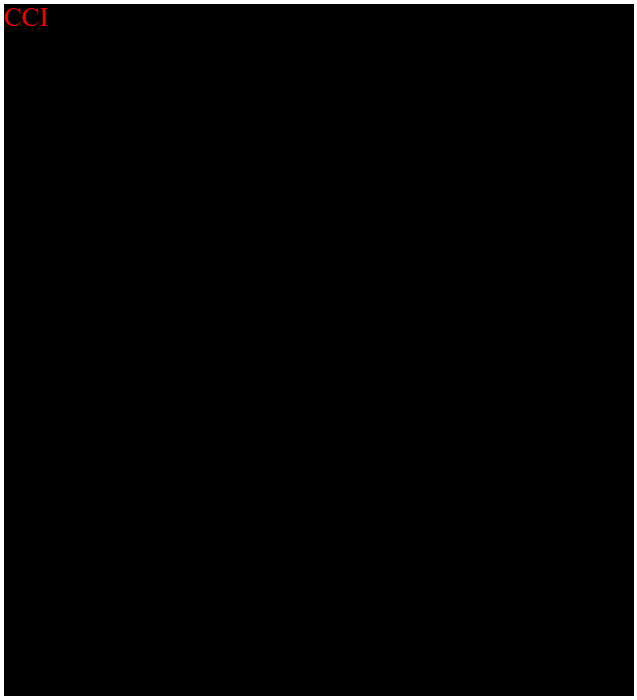
CCI


CCI


CCI


CCI

CCI



12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	A participant will be considered to have completed the study if the participant dies during the study treatment period or follow-up period, whichever is sooner, or is still in followup at the time of the final analysis. • A participant will be considered to have withdrawn from the study if the participant has not died and is lost to follow-up, has withdrawn consent, at the investigator's discretion is no longer being followed or if the study is closed/terminated. • Participants who discontinue will not be replaced in this study. All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

12.7.2. Handling of Missing Data

Element	Reporting Detail
General	• 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 participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

12.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. However, where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases (see Section 12.4.1) or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis). In addition, imputed dates are not used for deriving the last contact date in overall survival analysis dataset.
Adverse Events	• Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. • Partial dates for AE recorded in the CRF will be imputed using the following conventions: Missing start day: • If study treatment start date is missing (i.e. participant did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: ○ If month and year of start date = month and year of study treatment start date then

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>▪ 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.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant 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.</td></tr>
<tr><td>Missing stop day</td><td>Last day of the month will be used.</td></tr>
<tr><td>Missing stop day and month</td><td>No Imputation</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
<tr><td>Concomitant Medications/ Blood Supportive Products</td><td>• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
<table>
<tr><td>Missing start day</td><td>• If study treatment start date is missing (i.e. participant 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.</td></tr>
<tr><td>Missing start day and month</td><td>• If study treatment start date is missing (i.e. participant 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.
• Else set start date = January 1.</td></tr>
<tr><td>Missing end day</td><td>A '28/29/30/31' will be used for the day (dependent on the month and year)</td></tr>
<tr><td>Missing end day and month</td><td>A '31' will be used for the day and 'Dec' will be used for the month.</td></tr>
<tr><td>Completely missing start/end date</td><td>No imputation</td></tr>
</table>
</td></tr>
</table>

Element	Reporting Detail

New Anti-Cancer Therapy/ Radiotherapy/ Surgical Procedures for Efficacy Evaluation (e.g., response rate, time to event)	• Completely missing start dates will remain missing, with no imputation applied;
	• Partial start dates will be imputed using the following convention:
	  • If both month and day are missing, no imputation will be applied;
	  • If only day is missing:
	  ○ If the month of partial date is the same as the month of last dosing date, minimum of (last dosing date + 1, last day of the month) will be used for the day;
	  ○ If the month of partial date is the same as the month of last disease assessment and the last disease assessment is PD, minimum of (last date of disease assessment + 1, last day of the month) will be used for the day;
	  ○ If both conditions above are met, the later date will be used for the day;
	  ○ Otherwise, a '01' will be used for the day;
	• Completely or partial missing end dates will remain missing, with no imputation applied;

ECG	• Missing baseline values are assumed to have baseline value <450 for QTc

12.8. Appendix 8: Values of Potential Clinical Importance

To identify values of potential clinical importance, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v [5.0]) will be used to assign grades for laboratory parameters including clinical chemistry, hematology, liver function tests, QTc (Fridericia's) values, LVEF and vital signs (heart rate, blood pressure, temperature).

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.

12.9. Appendix 9: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
ADA	Anti-drug antibodies
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CR	Complete Response
DOB	Date of Birth
DOR	Duration of Response
DP	Decimal Places
eCRF	Electronic Case Record Form
FA	Final Analysis
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
(i)CR	Complete Response as per (i)RECIST 1.1
(i)PR	Partial Response as per (i)RECIST 1.1
iUPD	Unconfirmed Progressive disease as per iRECIST 1.1
iCPD	Confirmed Progressive Disease as per iRECIST 1.1
(i)SD	Stable Disease as per (i)RECIST 1.1
(i)PFS	Progression free survival as per (i)RECIST 1.1
(i)ORR	Overall response rate as per (i)RECIST 1.1
(i)DOR	Duration of Response as per (i)RECIST 1.1
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
ITT	Intent-To-Treat
IV	Intravenous
IWRS	Interactive web response system
LFT	Liver function test
LVEF	Left ventricular ejection fraction
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NSCLC	Non-small-cell lung cancer
CCI	[redacted]
ORR	Overall Response Rate
OS	Overall Survival
PA	Primary Analysis
PCI	Potential Clinical Importance

Abbreviation	Description
PD	Progressive Disease
PFS	Progression Free Survival
PDMP	Protocol Deviation Management Plan
CCI [redacted]	
PK	Pharmacokinetic
PP	Per Protocol
PR	Partial Response
PRO	Patient-reported outcome
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
QoL	Quality of Life
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RECIST	Response evaluation criteria in solid tumours
SAC	Statistical Analysis Complete
SD	Stable Disease
SDTM	Study Data Tabulation Model
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
WinNonLin

12.10. Appendix 10: List of Data Displays

12.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.23	
Efficacy	2.1 to 2.12	2.1 to 2.6
Safety	3.1 to 3.34	3.1 to 3.2
Pharmacokinetic	4.1 to 4.4	4.1 to 4.6
Patient Reported Outcome	5.1 to 5.12	5.1 to 5.6
Section	**Listings**	
ICH Listings	1 to 35	
Other Listings	36 to 44	

12.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Section 12.11: Example Mock Shells for Data Displays.

Section	Figure	Table
Safety		SAFE_Tn
Patient Reported Outcome	PRO_Fn	PRO_Tn

12.10.3. Deliverables

Delivery	Description
Part 1	Futility analysis
IDMC	Independent Data Monitoring Committee Open session
PA	Primary Analysis
FA	Final Statistical Analysis Complete

12.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT/Safety	ES8	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/PA. FA,(Headline)
1.2.	Safety	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	PART1, IDMC/ PA. FA, (Headline)
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	PART1, IDMC/ PA. FA,
1.4.	ITT/Safety	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.5.	Screened	SP1	Summary of Study Populations	IDSL	PART1, PA. FA,
Protocol Deviation					
1.6.	ITT/Safety	DV1	Summary of Protocol Deviations	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population Separate the page by important and non-important deviations	PART1, PA. FA,

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographics					
1.7.	ITT/Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include baseline stratification factors Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA, (Headline)
1.8.	ITT/Safety	DM11	Summary of Age Ranges	EudraCT Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.9.	ITT/Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
Prior and Concomitant Medications					
1.10.	ITT/Safety	MH1	Summary of Past Medical Conditions	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.11.	ITT/Safety	MH1	Summary of Current Medical Conditions	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.12.	ITT/Safety	CM1	Summary of Concomitant Medications	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	PART1, PA. FA,
Disease Characteristics					
1.13.	ITT	DC1	Summary of Disease Characteristics at Initial Diagnosis	ICH E3	IDMC/ PA. FA,

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.14.	ITT	DC2	Summary of Disease Characteristics at Baseline	ICH E3 Add definitions for progression and recurrence	IDMC/ PA. FA, (Headline)
1.15.	ITT	MD1	Summary of Metastatic Disease at Screening		IDMC/ PA. FA,
1.16.	ITT	LA1	Summary of Disease Burden at Baseline	ICH E3	IDMC/ PA. FA,
Anti-Cancer Therapy					
1.17.	ITT/Safety	AC1	Summary of Prior Anti-Cancer Therapy	IDSL Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.18.	ITT/Safety	CM1	Summary of Prior Dictionary Coded Anti-Cancer Therapy	IDSL Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.19.	ITT/Safety	AC3	Summary of Number of Prior Anti-Cancer Therapy Regimens	IDSL Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
1.20.	ITT/Safety	FAC1	Summary of Follow-up Anti-Cancer Therapy	IDSL Part 1 is based on Safety population Part 2 is based on ITT population	PART1, PA. FA,

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Surgical/Medical Procedures					
1.21.	ITT/Safety	OSP1	Summary of Prior Surgical Procedures	IDSL Part 1 is based on Safety population Part 2 is based on ITT population	PART1, IDMC/ PA. FA,
Substance Use					
1.22.	ITT	SU1	Summary of Substance Use	IDSL	IDMC/ PA. FA,
Follow-up					
1.23.	ITT	FAC2	Summary of Duration of Follow-up		PA. FA,

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Responses					
2.1.	ITT /Safety	RE1a	Summary of Confirmed Investigator-Assessed Best Response (RECIST1.1)	Add rows for DCR (CR+PR+SD), Odds ratio for DCR, 95% CI and p-Value Part 1 is based on Safety population Part 2 is based on ITT population	PART1, PA. FA,(Headline)
2.2.	ITT	RE1a	Summary of Confirmed Investigator-Assessed Best Response (iRECIST Criteria)	Add rows for DCR (CR+PR+SD), Odds ratio for DCR, 95% CI and p-Value	PA. FA,
2.3.	ITT	RE2	Summary of Investigator Assessed Response Rate with confirmation (RECIST1.1 Criteria) by Stratification Factors	• Histology (squamous vs. non squamous) and line of PD(L)1 therapy (1st vs. 2nd line). • Add Count and percentages for DCR (CR+PR+SD)	PA. FA,
2.4.	ITT	RE2	Summary of Investigator Assessed Response Rate with confirmation (iRECIST Criteria) by Stratification Factors	Add Count and percentages for DCR (CR+PR+SD)	PA. FA,

Time-to-event Endpoints					
2.5.	ITT	TTE3	Summary of Kaplan-Meier Estimates of Progression-Free Survival	Using RECIST1.1 followed by iRECIST on next page Do not report p-values	PA. FA,(Headline)
2.6.	ITT	TTE3	Summary of Kaplan-Meier Estimates of Overall Survival	Do not report p-values	PA. FA,(Headline)
2.7.	ITT	TTE6	Summary of Kaplan-Meier Estimates of Overall Survival at 12 and 18 Months		PA. FA,
2.8.	ITT	TTE1	Summary of Kaplan-Meier Estimates of Duration of Response in Subjects with Objective Response	Page by RECIST1.1 then iRECIST	PA. FA,(Headline)
2.9.	ITT	TTE4	Summary of Cox Proportional Hazards Regression Model for Overall Survival	Remove p-value column Include a row for predictive probability of Phase 3 success as the last segment	PA. FA,(Headline)
2.10.			Model Diagnostic SAS outputs from Cox Proportional Hazards model for Overall Survival	RTF format of SAS results output	PA. FA,
2.11.	ITT	TTE4	Summary of Cox Proportional Hazards Regression Model for Overall Survival (Sensitivity Analysis for Adjusting the Impact of COVID 19)		PA. FA,
2.12.	ITT	TTE4	Summary of Cox Proportional Hazards Regression Model for Progression Free Survival	Remove p-value column Page by RECIST 1.1 then iRECIST	PA. FA,

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Responses					
2.1.	ITT /Safety	RE1a	Summary of Confirmed Investigator-Assessed Best Response (RECIST1.1)	Add rows for DCR (CR+PR+SD), Odds ratio for DCR, 95% CI and p-Value Part 1 is based on Safety population Part 2 is based on ITT population	PART1, PA. FA,(Headline)
2.2.	ITT	RE1a	Summary of Confirmed Investigator-Assessed Best Response (iRECIST Criteria)	Add rows for DCR (CR+PR+SD), Odds ratio for DCR, 95% CI and p-Value	PA. FA,
2.3.	ITT	RE2	Summary of Investigator Assessed Response Rate with confirmation (RECIST1.1 Criteria) by Stratification Factors	• Histology (squamous vs. non squamous) and line of PD(L)1 therapy (1st vs. 2nd line). • Add Count and percentages for DCR (CR+PR+SD)	PA. FA,
2.4.	ITT	RE2	Summary of Investigator Assessed Response Rate with confirmation (iRECIST Criteria) by Stratification Factors	Add Count and percentages for DCR (CR+PR+SD)	PA. FA,

Time-to-event Endpoints					
2.5.	ITT	TTE3	Summary of Kaplan-Meier Estimates of Progression-Free Survival	Using RECIST1.1 followed by iRECIST on next page Do not report p-values	PA. FA,(Headline)
2.6.	ITT	TTE3	Summary of Kaplan-Meier Estimates of Overall Survival	Do not report p-values	PA. FA,(Headline)
2.7.	ITT	TTE6	Summary of Kaplan-Meier Estimates of Overall Survival at 12 and 18 Months		PA. FA,
2.8.	ITT	TTE1	Summary of Kaplan-Meier Estimates of Duration of Response in Subjects with Objective Response	Page by RECIST1.1 then iRECIST	PA. FA,(Headline)
2.9.	ITT	TTE4	Summary of Cox Proportional Hazards Regression Model for Overall Survival	Remove p-value column Include a row for predictive probability of Phase 3 success as the last segment	PA. FA,(Headline)
2.10.			Model Diagnostic SAS outputs from Cox Proportional Hazards model for Overall Survival	RTF format of SAS results output	PA. FA,
2.11.	ITT	TTE4	Summary of Cox Proportional Hazards Regression Model for Overall Survival (Sensitivity Analysis for Adjusting the Impact of COVID 19)		PA. FA,
2.12.	ITT	TTE4	Summary of Cox Proportional Hazards Regression Model for Progression Free Survival	Remove p-value column Page by RECIST 1.1 then iRECIST	PA. FA,

12.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Response					
2.1	ITT	RE8a	Investigator-Assessed Maximum Percent Reduction from Baseline in Tumor Measurement (RECIST1.1)		PART1, PA. FA,
Time-to-Event Endpoints					
2.2.	ITT	TTE10	Graph of Kaplan Meier Survival Curves for Progression Free Survival with 95% Confidence Band	Page by RECIST1.1 then iRECIST.	PA. FA,(Headline)
2.3.	ITT	TTE10	Graph of Kaplan Meier Curves for Overall Survival	Include line at 12 months and 18 months to approximate the rate and 95% CI.	PA. FA,(Headline)
2.4.	ITT	TTE10	Graph of Kaplan Meier Curves for Duration of Response in Subjects with Objective Response	Page by RECIST1.1 then iRECIST	PA. FA,
2.5.	ITT	TTE11	Forest Plot of r Overall Survival by Subgroup		PA. FA,(Headline)
2.6.	ITT	TTE11	Forest Plot of Progression Free Survival by RECIST1.1. by Subgroup		PA. FA,

12.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE5B	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Grade		PART1, PA. FA,
3.2.	Safety	OAE07	Summary of Treatment Emergent Adverse Events by Preferred Term and Maximum Grade		PART1, PA. FA, (Headline)
3.3.	Safety	AE13	Treatment Emergent Adverse Events Overview	Include Any AE, AEs related to study treatment,leading to permanent discontinuation of study treatment,leading to dose reduction,leading to dose interruption/delay, Any SAE,SAEs related to study treatment,Fatal SAEs,Fatal SAEs related to study treatment Add an additional row to indicate frequency and percentage of Treatment Related AE's of grade 3+4+5	PART1, PA. FA, (Headline)
3.4.	Safety	AE3	Summary of Common (>=5%) Grade 3-5 Treatment Emergent Adverse Events by Overall Frequency		PART1, PA. FA, (Headline)
3.5.	Safety	OAE01	Summary All Drug-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term and Maximum Grade		PART1, PA. FA,

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	Safety	AE15	Summary of Common (>=5%) Non-serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)		PART1, PA. FA,
3.7.	Safety	AE3	Summary of Common (>=5%) Drug-Related Grade 3-5 Treatment Emergent Adverse Events by Overall Frequency		PART1, PA. FA,
3.8.	Safety	AE3	Summary of Non-Serious Drug-Related Treatment Emergent Adverse Events by Overall Frequency		PART1, PA. FA,
Adverse Events of Special Interest					
3.9.	Safety	OAE01	Summary of Adverse Event or Condition of Special interest by Preferred Term and Maximum Grade		PART1, PA. FA,
3.10.	Safety	ESI2a	Summary of Onset and Duration of the First Occurrence of AE of Special Interest		PART1, PA. FA,
Serious and Other Significant Adverse Events					
3.11.	Safety	AE16	Summary of Serious Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	PART1, PA. FA, (Headline)
3.12.	Safety	AE3	Summary of Treatment Emergent Adverse Events Leading to Permanent Discontinuation of Study Treatment by Preferred Term		PART1, PA. FA,
Deaths					
3.13.	Safety	DTH1a	Summary of Deaths	IDSL	PART1, PA. FA, (Headline)

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
3.14.	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3	PART1, PA. FA,
3.15.	Safety	OLB9C	Summary of Worst Case Chemistry Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3	PART1, PA. FA,
3.16.	Safety	OLB11C	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	PART1, PA. FA,
Laboratory: Hematology					
3.17.	Safety	LB1	Summary of Hematology Changes from Baseline	ICH E3	PART1, PA. FA,
3.18.	Safety	OLB9C	Summary of Worst Case Hematology Results by Maximum Grade Increase Post-Baseline Relative to Baseline	ICH E3	PART1, PA. FA,
3.19.	Safety	OLB11C	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	PART1, PA. FA,

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Urinalysis					
3.20.	Safety	LB1	Summary of Urinalysis Results	ICH E3	PART1, PA. FA,
3.21.	Safety	OUR1B	Summary of Worst Case Urinalysis Results (Discrete or Character Values) Post-Baseline Relative to Baseline	ICH E3	PART1, PA. FA,
Laboratory: Hepatobiliary (Liver)					
3.22.	Safety	OLIVER1	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	PART1, PA. FA,
Vital Signs					
3.23.	Safety	OVT1B	Summary of Changes in Vital Signs from Baseline		PART1, PA. FA,
Exposure/Dose Modifications					
3.24.	Safety	SAFE_T1	Summary of Exposure to Treatment	Add a footnote defining the “Cycle”	PART1, PA. FA, (Headline)
3.25.	Safety	ODMOD4	Summary of Missed Doses by Component	Exclude the last segment “Number of Subjects with Missed Doses by Planned Time”	PART1, PA. FA,

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.26.	Safety	ODMOD1	Summary of Dose Reductions	Exclude the last segment "Number of Subjects with Dose Reduction by Planned Time". Count number of participants and total number of reductions if either component is reduced. Summarise details on number and reason by component in separate rows	PART1, PA. FA,
3.27.	Safety	ODMOD3	Summary of Dose Delays	Exclude the last segment "Number of Subjects with Dose Delays by Planned Time". Count number of participants and total number of delays if either component is delayed. Summarise details on number, duration and reason by component in separate rows	PART1, PA. FA,
3.28.	Safety	ODMOD9	Summary of Incomplete Infusions	Exclude the last segment "Number of Subjects with Incomplete Infusions by Planned Time"	PART1, PA. FA,
3.29.	Safety	ODMOD16	Summary of Infusion Interruptions	Exclude the last segment" Number of Subjects with Infusion Interruptions by Planned Time"	PART1, PA. FA,

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Performance Status					
3.30.	Safety	PS1A	Summary of ECOG Performance Status	ICH E3	PART1, PA. FA,
Immunogenecity					
3.31.	Safety	IMM1	Summary of Positive Immunogenecity Results		PART1, PA. FA,
COVID-19 Assessments					
3.32.	Safety	PAN1	Summary of COVID-19 Assessments for Subjects with COVID-19 Adverse Events		PART1, PA. FA,
3.33.	Safety	PAN3	Summary of COVID-19 Symptoms for Subjects with COVID-19 Adverse Events		PART1, PA. FA,
Dose Limiting Toxicity (DLT					
3.34.	DLT Evaluable	AE19	Summary of Dose-Limiting Toxicities during the Determinative Period (DE Phase)		PART1

12.10.8. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
3.1.	Safety	OEX12	Plot of Duration of Study Treatment		PA. FA,
Laboratory					
3.2.	Safety	Liver9	Scatter Plot of Maximum Bilirubin versus Maximum ALT – eDISH		PA. FA,

12.10.9. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK01	Summary of GSK3359609 Plasma Concentration Time Data	IDSL	FA, SAC
4.2.	PK	PK01	Summary of Docetaxel Plasma Concentration Time Data	IDSL	FA, SAC
4.3.	PK	PK06	Summary of Derived GSK3359609 Pharmacokinetic Parameters (non-transformed and log-transformed)	IDSL	FA, SAC
4.4.	PK	PK06	Summary of Derived Docetaxel Parameters (non-transformed and log-transformed)	IDSL	FA, SAC

12.10.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
4.1.	PK	PK16a	Individual GSK3359609 Plasma Concentration-Time Plot by Subject (Linear and Semi-Log)	IDSL	FA, SAC
4.2.	PK	PK16a	Individual Docetaxel Plasma Concentration-Time Plot by Subject (Linear and Semi-Log)	IDSL	FA, SAC
4.3.	PK	PK17	Mean GSK3359609 Concentration-Time Plots (Linear and Semi-log)	IDSL	FA, SAC
4.4.	PK	PK17	Mean Docetaxel Concentration-Time Plots (Linear and Semi-log)	IDSL	FA, SAC
4.5.	PK	PK18	Median GSK3359609 Concentration-Time Plots (Linear and Semi-log)	IDSL	FA, SAC
4.6.	PK	PK18	Median Docetaxel Concentration-Time Plots (Linear and Semi-log)	IDSL	FA, SAC

12.10.11. Patient Reported Outcomes Tables

Patient Reported Outcome: Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
CCI [redacted]					

Patient Reported Outcome: Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
CCI					

Patient Reported Outcome: Tables					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
CCI					

12.10.12. Patient Reported Outcomes Figures

Patient Reported Outcome: Figures					
No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
CCI [redacted]					

12.10.13. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	Part1, IDMC/ PA. FA,
2.	ITT/Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	Part1, IDMC/ PA. FA,
3.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	Part1,IDMC/ PA. FA,
4.	ITT	TA1	Listing of Planned and Actual Treatments	IDSL	PA. FA,
Protocol Deviations					
5.	ITT/Safety	DV2	Listing of Important Protocol Deviations	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	Part1, PA. FA,
6.	ITT/Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	Part1, IDMC/ PA. FA,
Demographic and Baseline Characteristics					
7.	ITT/Safety	DM2	Listing of Demographic Characteristics	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	Part1, IDMC/ PA. FA,

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
8.	ITT/Safety	DM9	Listing of Race	ICH E3 Part 1 is based on Safety population Part 2 is based on ITT population	Part1, IDMC/ PA. FA,
Prior and Concomitant Medications					
9.	ITT/Safety	CP_CM3	Listing of Prior/Concomitant Medications	IDSL Part 1 is based on Safety population Part 2 is based on ITT population	Part1, PA. FA,
10.	ITT/Safety	MH2	Listing of Past/Current Medical Conditions	Oncology specific template to be used Part 1 is based on Safety population Part 2 is based on ITT population	Part1, IDMC/ PA. FA,
Exposure and Treatment Compliance					
11.	Safety	OEX8a	Listing of Exposure to Docetaxel	ICH E3	PA. FA,
12.	Safety	OEX8b	Listing of Exposure to GSK3359609	ICH E3	Part1, PA. FA,
13.	Safety	COMP2	Listing of Overall Compliance		Part1, IDMC/ PA. FA,
Dose Modifications					
14.	Safety	ODMOD10A	Listing of Dose Reductions	Exclude Cycle	Part1, PA. FA,

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
15.	Safety	ODMOD17A	Listing of Infusion Interruptions	Exclude Cycle	Part1, PA. FA,
16.	Safety	ODMOD14A	Listing of Incomplete Infusions	Exclude Cycle Day	Part1, PA. FA,
17.	Safety	ODMOD12A	Listing of Dose Delays	Exclude Cycle Day	Part1, PA. FA,
18.	Safety	ODMOD13A	Listing of Missed Doses	Exclude Cycle	Part1, PA. FA,
Response					
19.	ITT/Safety	LA5	Listing of Investigator Assessed Lesion Assessments (RECIST 1.1 Criteria)	Include Target Lesions,Non-Target Lesions and New Part 1 is based on Safety population Part 2 is based on ITT population	Part1, PA. FA,
20.	ITT	LA5	Listing of Investigator Assessed Lesion Assessments (iRECIST Criteria)	Include Target Lesions,Non-Target Lesions and New Lesions	PA. FA,
21.	ITT/Safety	RE5	Listing of Investigator Assessed Responses with confirmation (RECIST 1.1 Criteria)	Part 1 is based on Safety population Part 2 is based on ITT population	Part1, PA. FA,
22.	Safety/ITT	RE5	Listing of Investigator Assessed Responses with confirmation (iRECIST Criteria)	Part 1 is based on Safety population Part 2 is based on ITT population	Part1, PA. FA,
Adverse Events					
23.	Safety	AE8	Listing of All Adverse Events	ICH E3	Part1, PA. FA,
24.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	Part1, PA. FA,
25.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	Part1, PA. FA,

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events of Special Interest					
26.	Safety	AE8	Listing of AE of Special Interest		Part1, PA. FA,
Serious and Other Significant Adverse Events					
27.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	Part1, PA. FA,
28.	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	Part1, PA. FA,
Deaths					
29.	Safety	DTH3	Listing of Deaths	ICH E3	Part1, PA. FA,
Hepatobiliary (Liver)					
30.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	Part1, PA. FA,
31.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	Part1, PA. FA,
All Laboratory					
32.	Safety	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	Part1, PA. FA,
33.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	Part1, PA. FA,

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Performance Status					
34.	Safety	PS5A	Listing of Performance Status		Part1, PA. FA,
Dose-Limiting Toxicities					
35.	DLT Evaluable	MTD_DLDL1	Listing of Dose-Limiting Toxicities (DLT) during the determinative period (DE Phase)		Part1

12.10.14. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disease Characteristics					
36.	ITT	DC3	Listing of Disease Characteristics at Initial Diagnosis		IDMC/ PA. FA,
37.	ITT	DC4	Listing of Disease Characteristics at Screening		IDMC/ PA. FA,
Anti-Cancer Therapy					
38.	ITT	AC6	Listing of Prior Anti-Cancer Therapy		IDMC/ PA. FA,
39.	ITT	AC7	Listing of Prior Anti-Cancer Radiotherapy		IDMC/ PA. FA,
40.	ITT	FAC3	Listing of Follow-Up Anti-Cancer Therapy		PA. FA,
Surgical Procedures					
41.	ITT	OSP3	Listing of Prior Surgical Procedures		PA. FA,
Immunogenecity					
42.	Safety	IMM2	Listing of Immunogenicity Results		PA. FA,
PK					
43.	PK	PK07	Listing of Pharmacokinetic Concentration-Time Data by Analyte	IDSL	PA. FA,
44.	PK	PK13	Listing of Derived Pharmacokinetic Parameters by Analyte	IDSL	PA. FA,

12.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on request.

12.12. Appendix 12: SDAC REPORTING PLAN

GSK Protocol 205801 - GSK3359609 ENTREE Study

Version: Final
Date: 20 February 2020

13. INTRODUCTION

This document, the SDAC Reporting Plan for GSK Protocol 205801, describes SDAC's proposal for the initial content and structure of Independent Data Monitoring Committee (IDMC) reports. It includes general statistical analysis conventions and a detailed proposed table of contents. Mock tables, figures, and listings are provided in a companion document, the *SDAC Sample Report*.

This document is the final version of SDAC Reporting Plan for GSK Protocol 205801. The drafted version (and the companion *SDAC Sample Report*) has been distributed to the DMC and GSK prior to the first IDMC meeting for review and discussion.

The IDMC, SDAC, and GSK recognize that for the IDMC to effectively execute their responsibility to oversee the safety of subjects enrolled in the study, they will require interim reporting that meets their needs as those needs evolve over the duration of the studies. As such, this proposal is intended as a general guide for the content and structure of initial reports to be produced by SDAC for the IDMC and it is not intended to either limit the scope of the analyses the IDMC may request or to require a particular form or structure for an analysis. It is understood that the IDMC will have the final authority to specify, on an ongoing basis, the content and structure of the reports they receive.

13.1. References to External Documents

Where this document excerpts or references external documents, the following versions have been used:

- *IDMC Charter* (Version 001, dated December 19, 2018)
- *SDAC Sample Report* (dated September 20, 2016)
- *Study Protocol* (205801 Amendment #1 dated September 20, 2018)
- *Study RAP* (Statistical Analysis Plan Reporting and Analysis Plan dated December 13, 2018)
- *AESI Listing* (GSK3359609 AESI list FINAL 03Apr19 - Version 1.xlsx)

13.2. OVERVIEW OF ANALYSES SPECIFIED IN THE IDMC CHARTER

SDAC will prepare both open session and closed session reports containing summaries of safety and/or efficacy data for data review meetings starting when adequate data are available. Data review meetings will be held at least every 6 months, but more frequent meetings may be held.

As described in the *IDMC Charter*, the IDMC will review the following data for study 205801: "Summarized unblinded safety data including AEs, SAEs, immune-related adverse events (irAEs), adverse events of special interest (AESI), and laboratory data for all active substudies. Summarized unblinded efficacy data primary endpoints and selected

secondary endpoints such as ORR, PFS, etc. Note that if a substudy or treatment arm has been discontinued, this data will not require further review."

As such, the safety reports from each of the studies will contain, at a minimum, analyses of all adverse events, serious adverse events (including deaths and SUSARs if recorded), withdrawals due to adverse events, laboratory values, and available efficacy data. All IDMC recommendations will be made based on a review of the totality of evidence.

As stated in the *IDMC Charter*, Section 3.5*,* "At the planned interim analyses in the 205801 study, the IDMC may make the recommendation to halt an individual substudy or study treatment arm (other than SoC) due to safety concerns and/or lack of efficacy." Additionally, the IDMC may recommend the discontinuation of an experimental regimen based on the totality of evidence to protect the safety, in relation to efficacy, of participating subjects. As such, closed session reports will include primary interim efficacy measures. Open session reports will omit these analyses to preserve blinding.

The details of these reports are described in Section 13.4.

13.3. GENERAL SDAC REPORTING CONVENTIONS

13.3.1. Sample Report

The separate document titled *SDAC Sample Report* provides an example of IDMC report content and format for a single, fictitious protocol based on simulated data. This fictitious protocol is patterned after a typical cardiovascular study, and therefore the example analyses are not tailored to the specifics of this study's design.

Actual reports for the GSK 205801 study will include initial content as proposed in detail in Section 4 below.

In the remainder of this document, references in doubled square brackets are to pages of the *Sample Report* (e.g., [[Figure ACCR-1, p. 18]]).

13.3.2. Open and Closed Session Reports

SDAC will produce Closed Session and Open Session versions of IDMC reports.

Closed Session reports will include analyses of all relevant data by treatment group. These reports will be only for review by the IDMC and will not be shared with other parties prior to database lock for the study. Treatment groups will be identified by single-letter codes with assignment of codes to treatment arms provided to the IDMC members in a separate document. Codes will be consistent between reports over the life of the trial.

Open session reports will include displays of aggregate data only (no treatment group information) and so will be fully blinded. Open session reports will also *exclude* efficacy

analyses and any additional analyses requested by the IDMC on the basis of their unblinded review. Open session reports will be provided to all open session participants, including the IDMC and GSK.

13.3.3. General Analysis Conventions

Reports will include analyses of all randomized subjects restricted to (1) post-randomization event data and (2) baseline and post-randomization data from other sources. In particular, analyses will exclude subjects that are screened but not randomized and will exclude any adverse events occurring prior to randomization.

All analyses will be performed on an intention-to-treat basis with subjects analyzed as randomized irrespective of adherence to treatment. In particular, analyses will include data collected for subjects who discontinue treatment but remain on study.

In general, for follow-up data collected on a per-visit basis (*e.g.,* laboratory measurements and vital signs) that include a visit code and a visit date, analyses by scheduled visit will use the visit code rather than applying a windowing algorithm to the visit date, and unscheduled visits will be excluded. Analyses that aggregate postbaseline data (*e.g.,* plots showing numbers of subjects who *ever* had a post-baseline, abnormal value for a laboratory measurement) will use all post-baseline measurements, whether scheduled or unscheduled.

13.3.4. Graphical Conventions

The primary mode of presentation in SDAC IDMC reports is graphical; most presented graphics have supporting back-up tables in the Supporting Material section of the report (see *SDAC Sample Report*, p. 74).

Categorical data will be presented as simple or stacked bar charts where the height of the bar or bar segment, respectively, represents the percent of subjects in a particular category (e.g., see Gender, Race, and NYHA Class in [[Figure DEMO-1, p. 28]]). Continuous data will be presented as boxplots where the bottom whisker, bottom edge of the box, horizontal line through the box, top edge of the box, and top whisker indicate the 5th, 25th (Q1), 50th (median), 75th (Q3), and 95th percentiles of the data, respectively, and a plotting symbol indicates the mean (e.g., see Age and Left Ventricular Ejection Fraction in [[Figure DEMO-1, p.28]]).

Time-to-event data will be presented as Kaplan-Meier plots of cumulative incidence (e.g., [[Figure ENDPT-3, p. 71, top panel]]). In the Closed Session Reports, treatment comparisons for time-to-event analyses across different endpoints or for a single endpoint across different subgroups will be presented as forest plots showing point estimates and 95% confidence intervals (CIs) for hazard ratios (HRs), as in [[Figure ENDPT-4, p. 73]].

A section of Supporting Material [[p. 74]] will contain back-up tables for the graphical displays of the previous chapters. These tables will be cross-referenced to and from the corresponding graphical pages.

13.3.5. P-values

In the closed session report, p-values for treatment comparisons will be provided for most post-baseline analyses. These p-values should be viewed as screening tools, rather than formal hypothesis tests, as no adjustment will be made for multiple tests performed. Given the large number of tests to be considered, it would be expected that a number of p-values will appear statistically significant (<0.05) simply by chance.

Except where otherwise noted, p-value calculations for continuous or ordered categorical data will use the nonparametric Wilcoxon-rank sum test (or Kruskal-Wallis test as appropriate), p-values for dichotomous and unordered categorical data will use Pearson's chi-square test without continuity correction, and p-values for time-to-event data will use a log-rank test.

13.3.6. Use of Listings when Data Are Limited

The study is expected to enroll 105 patients in the initial treatment arms, but early IDMC reports may include displays incorporating limited data on a small number of randomized patients. The detailed table of contents below and the Sample Report companion to this document assume a sufficient amount of data to support the use of graphical and tabular summaries. However, for initial reports where data for some displays are very limited, listings may be more appropriate and useful. SDAC will exercise its judgment in its use of graphics and tables versus listings in initial reports. On an ongoing basis, the IDMC, in consultation with SDAC, will evaluate the relative suitability of listings alone, summaries supplemented by listings, and summaries alone to communicate the results of interim analyses, and SDAC will adapt its reporting accordingly.

13.3.7. Considerations for Analysis of Interim Data

IDMC reports will be based on data from interim snapshots of the study database and other interim sources of data. These sources are likely to include so-called “dirty” data: records that are incomplete, inconsistent, entered in error, not yet adjudicated or coded, and otherwise under query. As a general approach, SDAC will include all available data in interim analyses, implementing reasonable conventions to resolve inconsistencies and handle incomplete records while utilizing statistical approaches that are robust in the face of errors.

Detailed conventions for handling dirty data will be documented in the introductory material of IDMC reports, but general approaches will include:

- Removing implausible or impossible values or assuming an appropriate unit conversion (e.g., height of 180 inches)
- Using simple hierarchical definitions for potentially contradictory sources of information (e.g., calculating a death date using the adjudicated result if available and falling back on dates included in the clinical endpoint dataset, from fatal adverse event records in the adverse event dataset, etc.)
- Presenting uncoded adverse events (AEs) in a separate category using the investigator-supplied verbatim term in tables and listings

- Completing partial dates using a sensible algorithm (e.g., middle of month if day is missing; middle of year if day and month are missing; with appropriate truncation for dates known or likely to be postrandomization)
- Use of statistical techniques that are robust in the face of gross errors such as use of quantile-based descriptive statistics (medians, quartiles, and 5th and 95th percentiles) and non-parametric tests (Wilcoxon)

13.4. PROPOSED DETAILED TABLE OF CONTENTS

The list below represents the proposed content for the Closed Session Report. The Open Session Report will have similar content (with analyses for randomized trials performed in aggregate only without respect to treatment group) but will exclude certain analyses as indicated above.

In the following, references are given to representative examples of content in the *Sample Report,* though analyses in actual reports may be presented in a different form (*e.g.,* listings in place of summaries where data are limited). Example graphics are presented with two treatment groups, though graphics for GSK 205801 may be modified to include three or more contrasts as applicable (see *Sample Report, Chapter A3,* p. 127).

13.4.1. Accrual and Study Status

[See the Sample Report Chapter 1 *for illustrative examples.]*

- Subject accrual over time by treatment arm (line plot, with bar graph by month) [[Figure ACCR-1, p. 18]]
- Site accrual over time (line plot, with bar graph by month) [[Figure ACCR-2, p. 19]]
- Geographic distribution of randomized subjects and randomizing sites (bar graph, table) [[Figures ACCR3-4, pp. 20-21]]
- Accrual by stratification factors (squamous vs non-squamous, 1st vs 2nd line of PD(L) 1 therapy) (bar graph)
- Subject treatment status, and reasons for IP discontinuation (bar graphs) [[Figure STAT-1, p. 23]]
- Subject study/completion status, and reasons for early study termination (bar graphs) [[Figure STAT-1, p. 23]]
- Protocol violation/deviations (listing)

13.4.2. Baseline Characteristics

[See the Sample Report Chapter 2 *for illustrative examples.]*

- Demographics [age, gender, race, ethnicity] (boxplot, bar graphs) [[Figure DEMO-1, p. 28]]
- Medical history (bar graph) [[Figure MDHX-1, p. 29]]
- Concomitant medication use at baseline by coded category (table)

- Vital signs [temperature, pulse rate, respiratory rate, blood pressure] (boxplots) [[Figure VITB-1, p. 30]]
- Physical measurements [height, weight, BMI] (boxplots) [[Figure VITB-1, p. 30]]
- Baseline labs [[Figure LABB-1, p. 31]]

13.4.3. Adverse Events

[See the Sample Report Chapter 3 *for illustrative examples.]* Serious adverse events:

- Listing of deaths
- Overview [any SAE, any SAE possibly related to study treatment, SAE leading to IP and/or study discontinuation, any fatal SAE] (bar graph) [[Figure SAE-1, p. 33]]
- Tabulation by SOC and High Level Term/Preferred Term (tables) [[Table SAETAB, p. 35]]
- Listing of SAEs by subject (listing showing treatment group, subject ID, sex, age, country, randomization date, start and end day of event relative to randomization and treatment periods, MedDRA preferred term, action taken with respect to study drug) [[Figure AELISTING-1, p. 38]]

Adverse events (whether serious or non-serious) leading to study drug discontinuation:

- Overview (AEs leading to treatment discontinuation, study withdrawal, dose interruptions/reductions) (bar graph) [[Figure AE-1, p. 39]]
- AE frequency by MedDRA SOC (stacked bars indicating max severity) [[Figure AE-2, p. 40]]
- Most common AEs [by MedDRA PT/HLT] (stacked bars indicating max severity) [[Figure AE-3, p. 41]]
- AEs with a nominally significant treatment difference (closed session only) [[Figure AE-4, p. 42]]
- Tabulation of by SOC and PT/HLT (tables) [[Table AETAB, p. 43]

Immune-related adverse events (irAEs)

- irAEs as described in Section 7.2.1.1 and Table 8 (p. 41) of the *Study Protocol* (bar graphs) [[similar to Figure AE-2, p.40]]

Adverse events of Special Interest (bar graphs) [[similar to Figure AE-2, p. 40]]

- Subclasses of AEs provided to SDAC by GSK in *AESI LISTING*: ○ Pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal function, skin adverse reactions, other immune-mediated adverse events (see *AESI LISTING* for full specifications)
- Infusion-related reactions ○ (see *AESI LISTING* for full specifications)

13.4.4. Central Laboratory Measures

Open session reports will omit all laboratory results that may unblind the study sponsor; SDAC will communicate with GSK to establish any lab parameters to be omitted.

[See the Sample Report Chapter 4 *for illustrative examples.]* General laboratory presentation:

- Summary page for each set of tests showing the percent above and/or below thresholds, as appropriate, for each test in the set (bar charts, with stacked bars for categorical assessments and for LFT elevations categorized by multiples of ULN) [[Figure LFTABN-1, p.49]]
- Each laboratory measure by scheduled visit [[Figure LFT-1, p. 50]]: ○ For most lab tests, multiple panels: measurements at each visit (boxplot), change from baseline (boxplot), percent of subjects above and/or below thresholds (ULN, LLN, or other clinically defined values of concern) at each visit (bar graph)
    - ○ For ordered categorical results (*e.g.,* some urinalysis assessments): stacked bars indicating the percent of subjects in each category at each visit
    - ○ Categories of laboratory measures displayed using above presentation:
        - Hematology
        - Clinical chemistry
        - Urinalysis

13.4.5. Other Follow-up Measures

[See the Sample Report Chapter 5 *for illustrative examples.]*

- Vital signs [body temperature, pulse rate, respiratory rate, systolic and diastolic blood pressure] (box plots by visit, with change from baseline) [[Figure VIT-1, p. 60]]
- Physical measurements [weight, BMI] (boxplots) [[Figure VIT-3, p. 62]]
- Physical exam [clinically significant changes since previous visit] (listing)
- ECG interpretation (bar graph by visit) [[Figure ECG-1, p. 63]]
- ECG data [QT, QTcF RR, GR, PR, QRS] (box plots by visit, with change from baseline) [[Figure ECG-2, p. 64]]

13.4.6. Efficacy and Interim Analyses

As specified in Section 3.1 of the *Study RAP*, formal interim analyses will be conducted by SDAC and presented to the IDMC in closed session. These analyses will be triggered after approximately 45 total observed events in the combined experimental and SoC arms, with a minimum of 18 events in the experimental arm.

[See the Sample Report Chapter 6, Study Endpoints, *pp. 69-72 for illustrative examples]* Primary Efficacy Parameters:

- Predictive probability of Phase III study success for each treatment arm as described in Section 10.5.1 of the *Study Protocol* — if triggered by events.

Key secondary Efficacy Parameters

- All-cause mortality (overall survival) (Cumulative mortality, forest plot) [[ENDPT-3, p. 71; ENDPT-4, p.72]]
- Kaplan-Meier estimates of milestone survival rates at 12 and 18 months (forest plot) [[similar to ENDPT4, p. 72]]

Note: Shells can be found here:

https://biostat.wiscweb.wisc.edu/wp-content/uploads/sites/1008/2019/05/Sample_Report_Closed_20160920.pdf

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