Statistical Analysis Plan Version 5

Study ID: 213403

Study Official Title: A Randomized, Phase 2, Double-blind Study to Evaluate the Efficacy of Dostarlimab Plus Chemotherapy Versus Pembrolizumab Plus Chemotherapy in Metastatic Non-Squamous Non-Small Cell Lung Cancer

NCT ID: NCT04581824

Date of Document: 22-Aug-2024

Division	:	Worldwide Development
Information Type	:	Statistical Analysis Plan (SAP)

Title Page

Protocol Title: A Randomized, Phase 2, Double-blind Study to Evaluate the Efficacy of Dostarlimab Plus Chemotherapy versus Pembrolizumab Plus Chemotherapy in Metastatic Non-Squamous Non-Small Cell Lung Cancer

Protocol Number: 213403

Compound Number: GSK4057190 (Dostarlimab)

Short Title: Efficacy Comparison of Dostarlimab Plus Chemotherapy vs Pembrolizumab Plus Chemotherapy in Participants with Metastatic Non-squamous Non-small Cell Lung Cancer

Acronym: PERLA

Sponsor Name: GlaxoSmithKline Research & Development Limited

Regulatory Agency Identifier Number(s)

Registry	**ID**
IND Number	150997
EudraCT Number	2020-002327-11

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TABLE OF CONTENTS

PAGE

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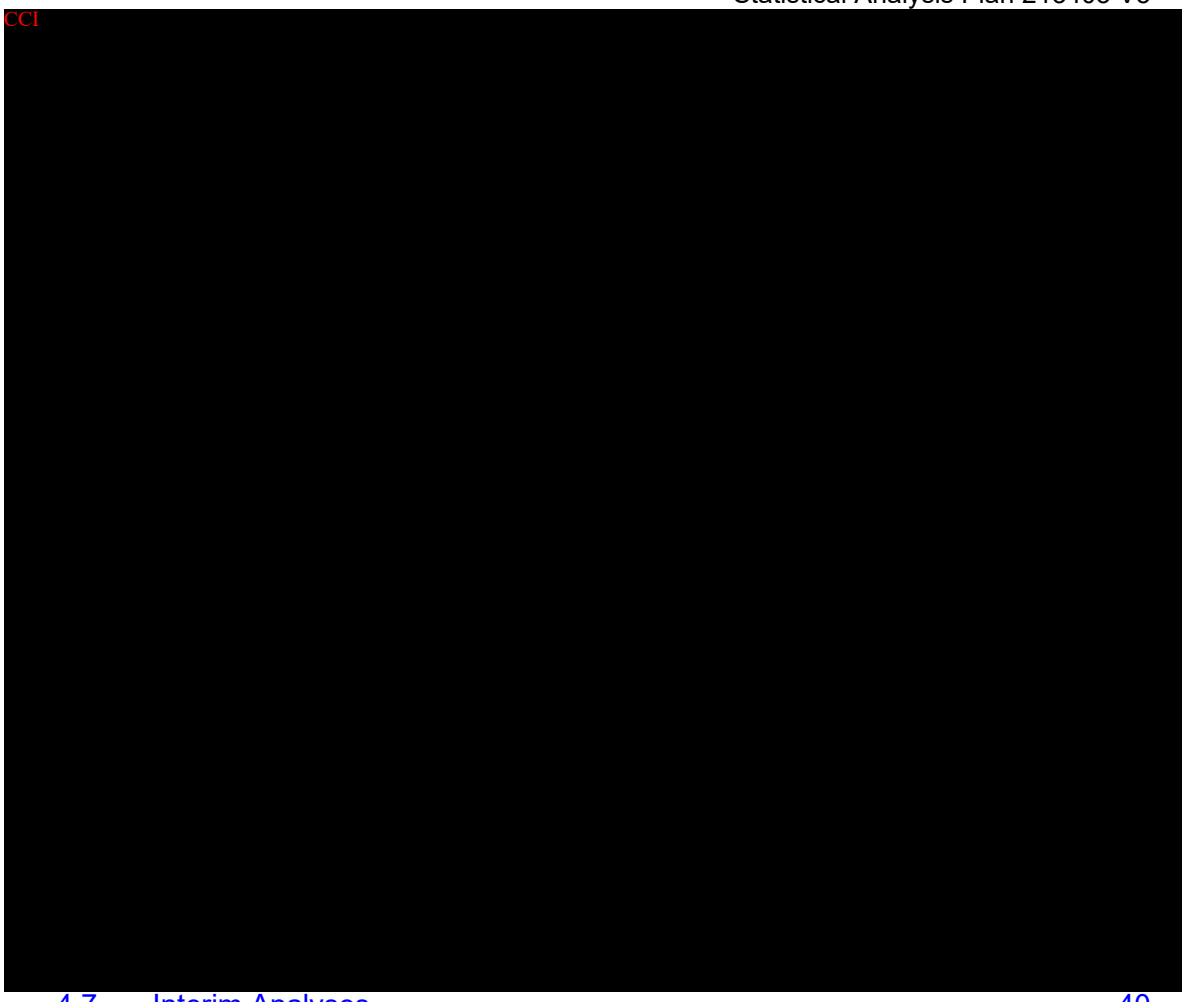

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LIST OF TABLES

PAGE

VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1	15 March 2022	Version 04 30 November 2021	Not Applicable	Original version
2	27 July 2022	Version 04 30 November 2021	CCI [redacted]	CCI [redacted]

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
3	07 June 2023	Version 05 14 February 2023	CCI [redacted]	CCI [redacted]

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
4	16 April 2024	Version 05 14 February 2023	CCI [redacted]	CCI [redacted]

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			CCI [redacted]	CCI [redacted]

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			CCI [redacted]	CCI [redacted]

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			CCI [redacted] CCI	
5	22 Aug 2024	Version 05 14 February 2024		

SAP Version	Document Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			CCI [redacted]	CCI [redacted]

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213403 (PERLA). Details of the final analyses are provided.

Descriptive study population analyses such as summary of demography and baseline characteristics and additional detail with regards to data handling conventions and the specification of data displays will be provided in the Output and Programming Specification (OPS) document.

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To compare the ORR of PD1 inhibitor dostarlimab vs pembrolizumab administered in combination with chemotherapy as evaluated using RECIST v1.1 based on BICR in participants with metastatic nonsquamous NSCLC, without a known EGFR, ALK, ROS1, or BRAF V600E mutation or other genomic aberration for which an approved targeted therapy is available, who have received no prior treatment of metastatic disease	• The primary efficacy endpoint ORR will be evaluated by RECIST v1.1 based on BICR and will be defined as the proportion of participants with BOR of CR or PR in the analysis population.
Secondary	
• To evaluate the following measures of clinical benefit of PD-1 inhibitor administered in combination with chemotherapy: – OS – PFS evaluated using RECIST v1.1 based on Investigator assessment	• OS will be defined as the time from the date of randomization to the date of death by any cause. • PFS will be evaluated using RECIST v1.1 based on Investigator assessment and will be defined as the time from the date of randomization to the date of PD or death by any cause, whichever occurs first.
• To evaluate the safety of PD-1 inhibitor in combination with chemotherapy	Assess the incidence of TEAEs, SAEs, irAEs, TEAEs leading to death, and AEs leading to discontinuation occurring while participants are on treatment or up to 90 days after the last dose of study treatment. Clinical laboratory parameters (hematology, chemistry, thyroid function, urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications will be collected.
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI	
Exploratory (continued)	
CCI	

Abbreviations: CCI ; ALK=anaplastic lymphoma kinase; BICR=blinded independent central review; CCI e; BRAF= proto-oncogene B-raf; CCI CCI ; CR=complete response;

CCI; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; CCI EOT=End-of-Treatment; CCI irAE=immune-related adverse event; CCI; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD=progressive disease; PD-1=programmed cell death protein 1; CCI PFS=progression-free survival; CCI RECIST=Response Evaluation Criteria in Solid Tumors; ROS-1=receptor tyrosine kinase-1; SAE=serious adverse event; TEAE=treatment-emergent adverse event; CCI

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1.1.2. Estimands

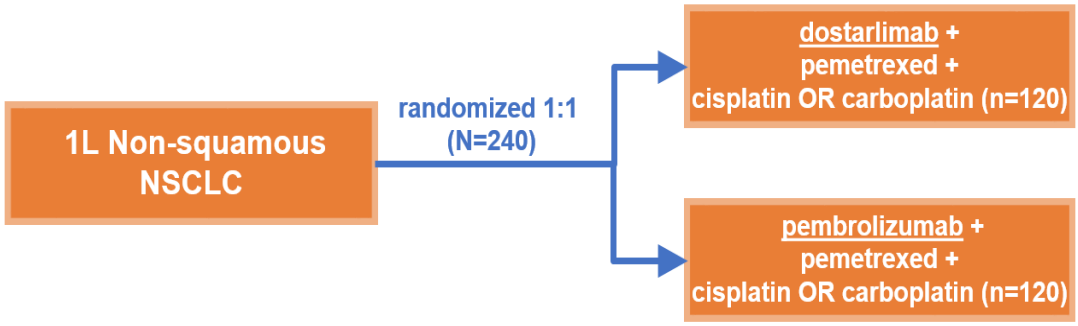
Table 2 Estimands

Objective	Estimand Category	Estimand			
		Population	Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
Primary Objective: To compare the ORR of dostarlimab vs pembrolizumab administered in combination with chemotherapy as evaluated using RECIST v1.1 based on BICR in participants with metastatic non-squamous NSCLC, without a known EGFR, ALK, ROS-1, or BRAF V600E mutation or other genomic aberration for which an approved targeted	Primary	Participants with metastatic non-squamous NSCLC, without a known EGFR, ALK, ROS-1, or BRAF V600E mutation or other genomic aberration for which an approved targeted therapy is available, who have received no prior treatment of metastatic disease	ORR	CCI	

Objective	Estimand Category	Estimand			
		Population	Variable/ Endpoint	Intercurrent Event Strategy	Population Level Summary Measure
therapy is available, who have received no prior treatment of metastatic disease					

1.2. Study Design

Overview of Study Design and Key Features



Abbreviations: 1L=first-line; NSCLC=non-small cell lung cancer.
Note: Both arms will be stratified by PD-L1 status (TPS <1% vs 1% to 49% vs ≥50%) and smoking status (never vs former/current)

Design Features	• This is a randomized, Phase 2, double-blind, 2-arm study to compare the efficacy and safety of PD-1 inhibitors dostarlimab and pembrolizumab, when administered in combination with chemotherapy, in male and female participants 18 years and older with non-squamous NSCLC without a known sensitizing epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), receptor tyrosine kinase-1 (ROS-1), or proto-oncogene B-raf (BRAF) V600E mutation or other genomic aberration for which an approved targeted therapy is available who have not received previous systemic anticancer therapy for metastatic disease. • Approximately 240 participants will be randomized in a 1:1 ratio into the dostarlimab plus chemotherapy arm or the pembrolizumab plus chemotherapy arm, such that approximately 120 evaluable participants in each of the 2 arms complete the study. • Randomization will be stratified by: ○ PD-L1 status of the tumor (TPS <1% versus 1% to 49% versus ≥50%);

Overview of Study Design and Key Features	
	○ Smoking status (never versus former/current). • The study consists of a Screening Period (Day -28 to Day -1) for completion of all Screening assessments and subsequent randomization, a Treatment Period, an EOT Visit (within 7 days of the decision to discontinue treatment for any reason), a Safety Follow-up Period with a visit at 30 (+7) and 90 (+7) days after the last dose of study treatment, and a Post-treatment Follow-up Period with assessments occurring 180 days after the last dose of study treatment and every 90 (±14) days thereafter, continuing until death, withdrawal of consent, or the end of study data collection. • The study will last approximately 5 years. During the Treatment Period participants will take part in up to 35 cycles with a visit frequency of Q3W (cycles are 21 [±3] days).
Study intervention	• Dostarlimab will be administered through a 30-minute infusion at a dose of 500 mg IV Q3W up to a maximum of 35 cycles total (approximately 24 months). • Pembrolizumab will be administered through a 30-minute infusion at a dose of 200 mg Q3W up to a maximum of 35 cycles total (approximately 24 months). • Chemotherapy (standard of care) will be administered to participants in both treatment arms: ○ Pemetrexed will be administered at 500 mg/m2 IV through a 10-minute IV infusion Q3W, up to a maximum of 35 cycles total (approximately 24 months). ○ Platinum chemotherapy (Cisplatin / Carboplatin) will be administered for the first 4 cycles only, following Pemetrexed administration. ▪ If selected by the Investigator, Cisplatin (75 mg/m2) will be administered via IV infusion (approximately 30 minutes after pemetrexed infusion) Q3W for the first 4 cycles. ▪ If selected by the Investigator, Carboplatin will be administered at area under the concentration-time curve 5 mg/mL/min (AUC 5 mg/mL/min) Q3W immediately following the pemetrexed infusion for 4 cycles.
Study intervention Assignment	• Participants who meet eligibility criteria will be randomized in a 1:1 ratio into the dostarlimab plus chemotherapy arm or the pembrolizumab plus chemotherapy arm, such that approximately 120 evaluable participants in each of the 2 arms complete the study. The randomization will be stratified by PD-L1 status of the tumor (TPS <1% vs 1% to 49% vs ≥50%) and smoking status (never vs former/current).

Overview of Study Design and Key Features	
Interim Analysis	• No formal interim analysis is planned for this study. CCI [redacted]
Supplementary Analysis	CCI [redacted]
End of Study Analysis	

2. STATISTICAL HYPOTHESES

The primary efficacy endpoint, ORR using RECIST v1.1 based on BICR, of dostarlimab plus chemotherapy is similar to that of pembrolizumab plus chemotherapy in participants with metastatic non-squamous NSCLC without a known EGFR, ALK, ROS-1, or BRAF V600E mutation or other genomic aberration for which an approved targeted therapy is available and who have not received prior treatment of metastatic disease.

2.1. Multiplicity Adjustment

CCI [redacted]

3. ANALYSIS SETS

The analysis sets are presented in Table 4.

Table 3 Analysis Sets

Analysis Set	
Screened	CCI [redacted]
Enrolled	
Intent-to-treat (ITT)	
Response Evaluable	
Per protocol (PP)	

Analysis Set	Definition / Criteria	Analyses Evaluated
Safety	CCI	
CCI		

1. CCI

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The ITT Set will be used for all Study Population analyses and Efficacy analyses and the Safety Analysis Set will be used for all safety analyses, unless otherwise stated.

Analysis and summaries performed on the ITT set will be presented by treatment assigned to the participant during randomization unless otherwise specified. CCI

4.1.2. Baseline Definition

CCI [redacted]

4.1.3. Multicenter Studies

In this multicenter global study, enrolment will be presented by country and site.

CCI [redacted]

4.1.4. Visit Windows

It is expected that all visits should occur according to the protocol schedule. CCI [redacted]

4.1.5. Study Population Summaries

The OPS document will provide additional details regarding the participant disposition and study population summaries, including, but not limited to the following:

- Participant status and disposition
- Treatment status and reasons for discontinuation of study treatment
- Screen status and reasons for screen failures
- Participants by country and site ID
- Important protocol deviations
- Study populations
- Demographics and baseline characteristics (including age, gender, ethnicity, race, and stratification factors: smoking status and PD-L1 status)
- Medical history / physical exam
- Advanced/Metastatic NSCLC history
- Prior anti-cancer therapy, prior radiotherapy and prior surgery
- Subsequent anti-cancer therapy
- Prior and concomitant medications
- Concomitant procedures

4.2. Primary Endpoint Analyses

The primary efficacy endpoint objective response rate (ORR) will be evaluated by RECIST v1.1 based on blinded independent central review (BICR). The primary analysis of ORR will be based on the ITT population, and a supportive sensitivity analysis will be performed on the response evaluable population and per-protocol population.

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4.2.1. Definition of endpoint

ORR per RECIST v1.1 is defined as the proportion of patients who have a complete response (CR) or partial response (PR) as their best overall response (BOR) based on BICR.

Best Overall Response (BOR)

The best overall response is the best response recorded from the date of randomization until disease progression or initiation of new anti-cancer therapy, whichever is earlier, as assessed by the BICR per RECIST v1.1, using all scans regardless of whether they were scheduled or not. The order from best to worst of the available responses is CR, PR, stable disease (SD), progressive disease (PD) and not evaluable (NE). In order to assign a BOR of CR or PR, a participant initial response must be confirmed by repeat assessment performed no less than 4 weeks after the initial criteria for response were met.

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4.2.2. Main analytical approach

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[redacted]

4.2.3. Sensitivity analyses

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4.3. Secondary Endpoints Analyses

The secondary efficacy endpoints overall survival (OS) and progression free survival (PFS) using RECIST v1.1 based on Investigator assessment will be evaluated. They will be summarized using the ITT population.

4.3.1. Definition of endpoints

4.3.1.1. Overall Survival (OS)

Overall Survival (OS), defined as the interval of time (in months) from randomization to the date of death due to any cause, regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy.

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4.3.1.2. Progression-Free Survival per RECIST v1.1 (PFS)

Progression-free survival (PFS) per RECIST v1.1 based on investigator assessment, defined as the interval of time (in months) between the date of randomization and the earlier of the date of disease progression (PD) as assessed by the investigator per RECIST 1.1 criteria and the date of death due to any cause.

Determination of dates of PFS events and dates for censoring are described in Table 4.

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4.3.2. Main analytical approach

4.3.2.1. Overall Survival (OS)

CCI

[redacted]

4.3.2.2. Progression-Free Survival per RECIST v1.1 (PFS)

CCI

[redacted]

CCI [redacted]

4.4. Supportive Secondary Endpoint(s)

4.4.1. Adverse Events/Serious Adverse Events

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

CCI [redacted]

For reporting, adverse events will be coded using the standard MedDRA coding dictionary CCI [redacted] Adverse events will be graded by the investigator according to the NCI-CTCAE, Version 5.0. A Standardized MedDRA Query (SMQ) will be used to identify all COVID-19 AEs.

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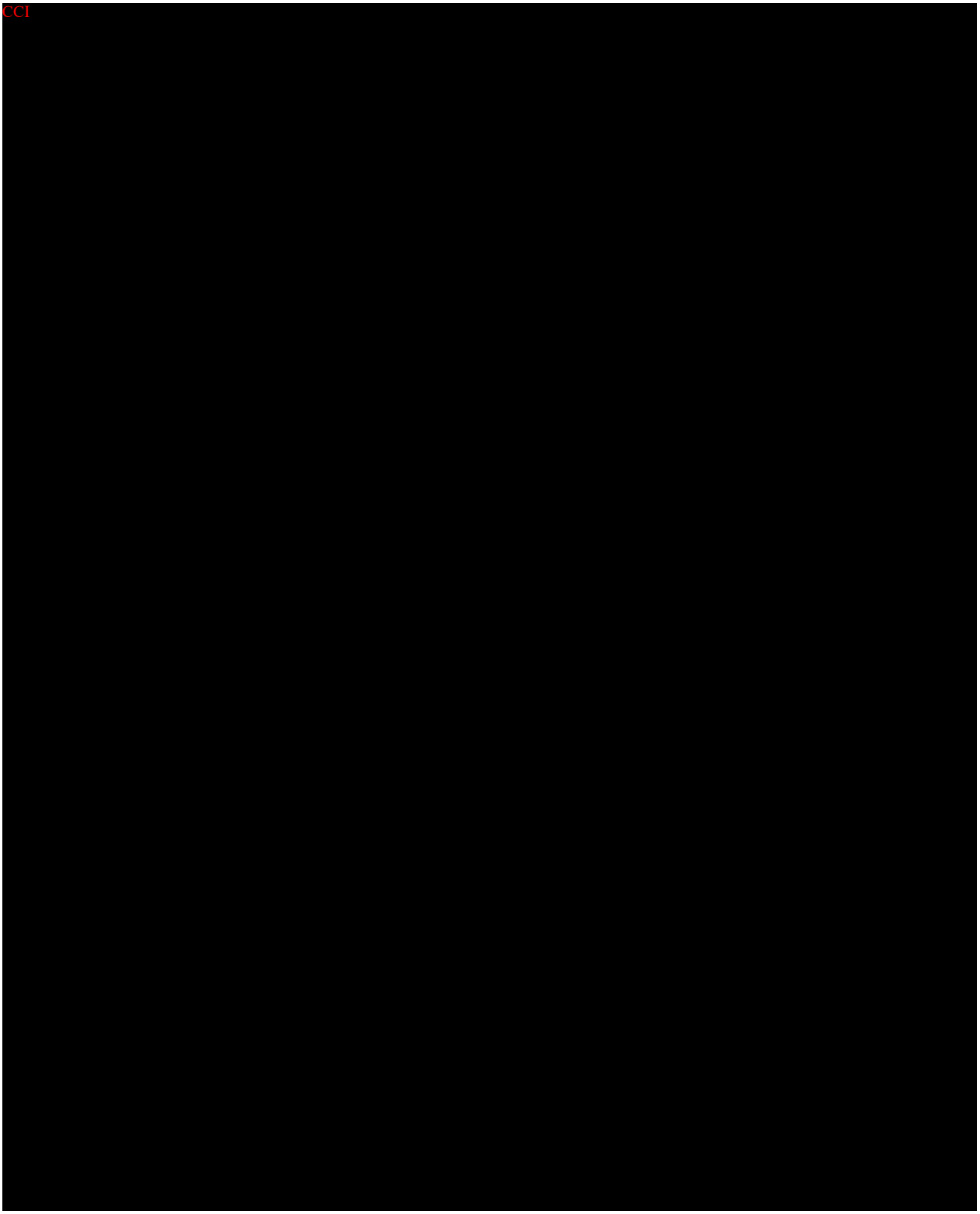

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4.5. Exploratory Endpoints Analyses

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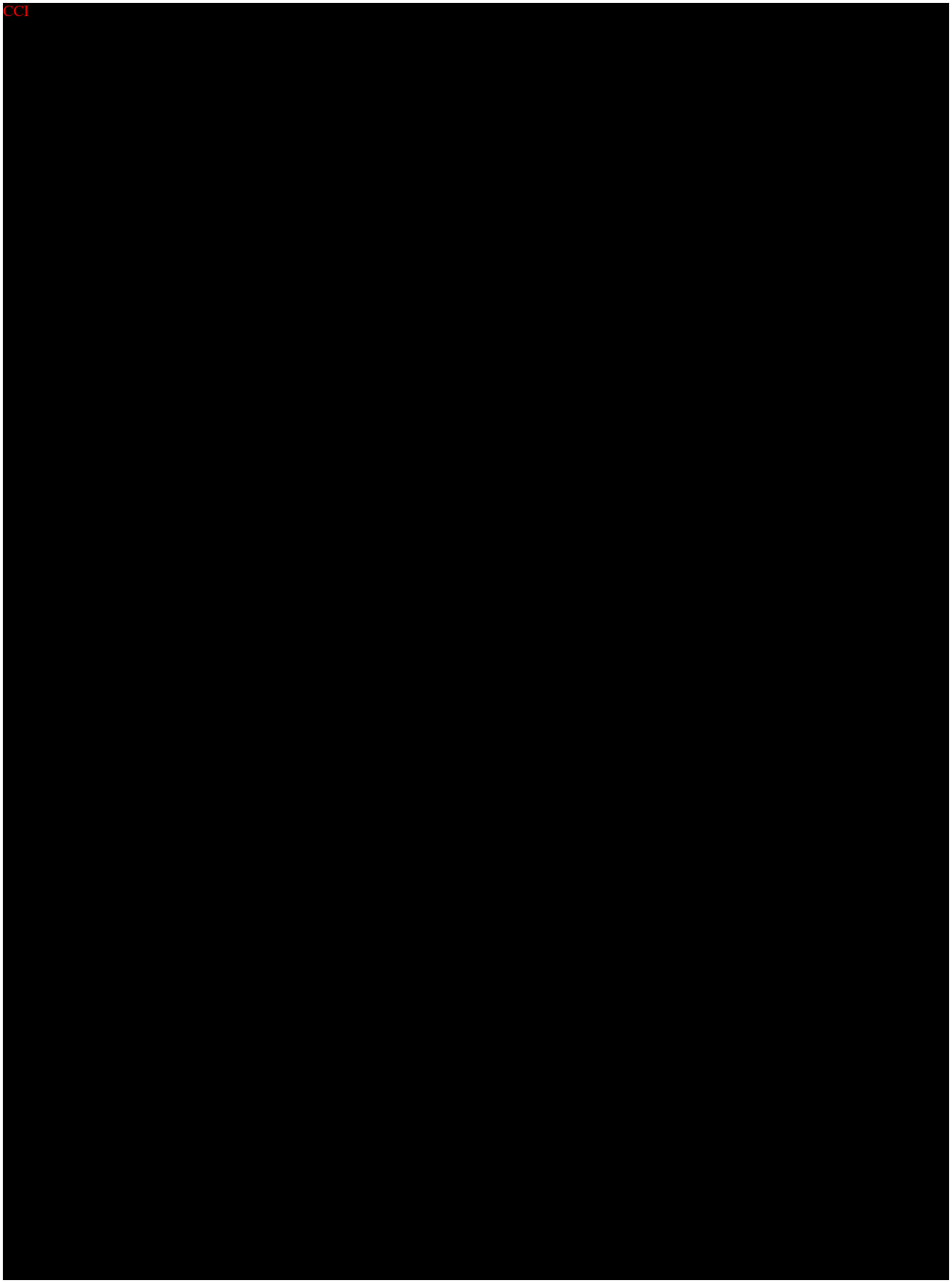

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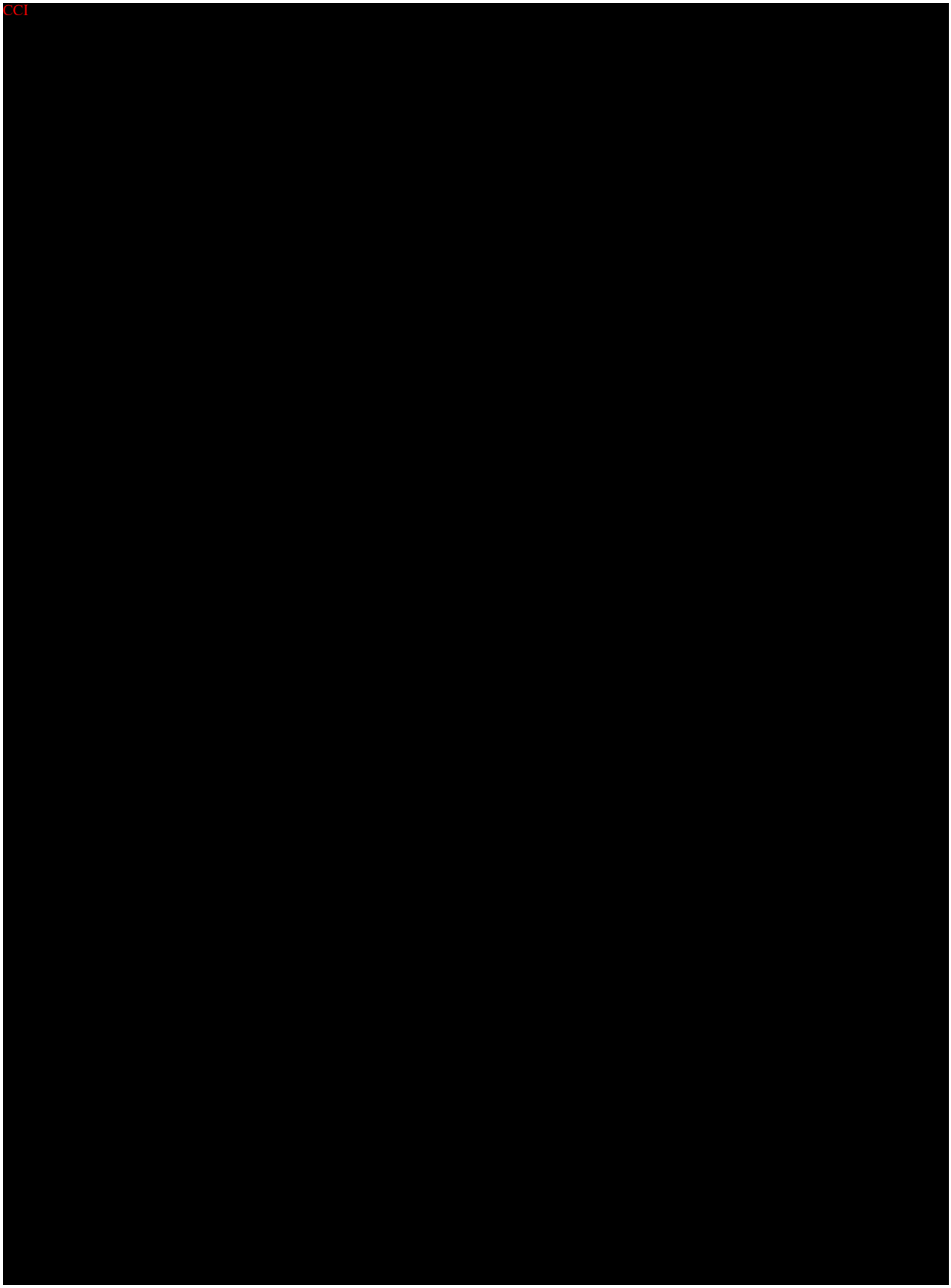

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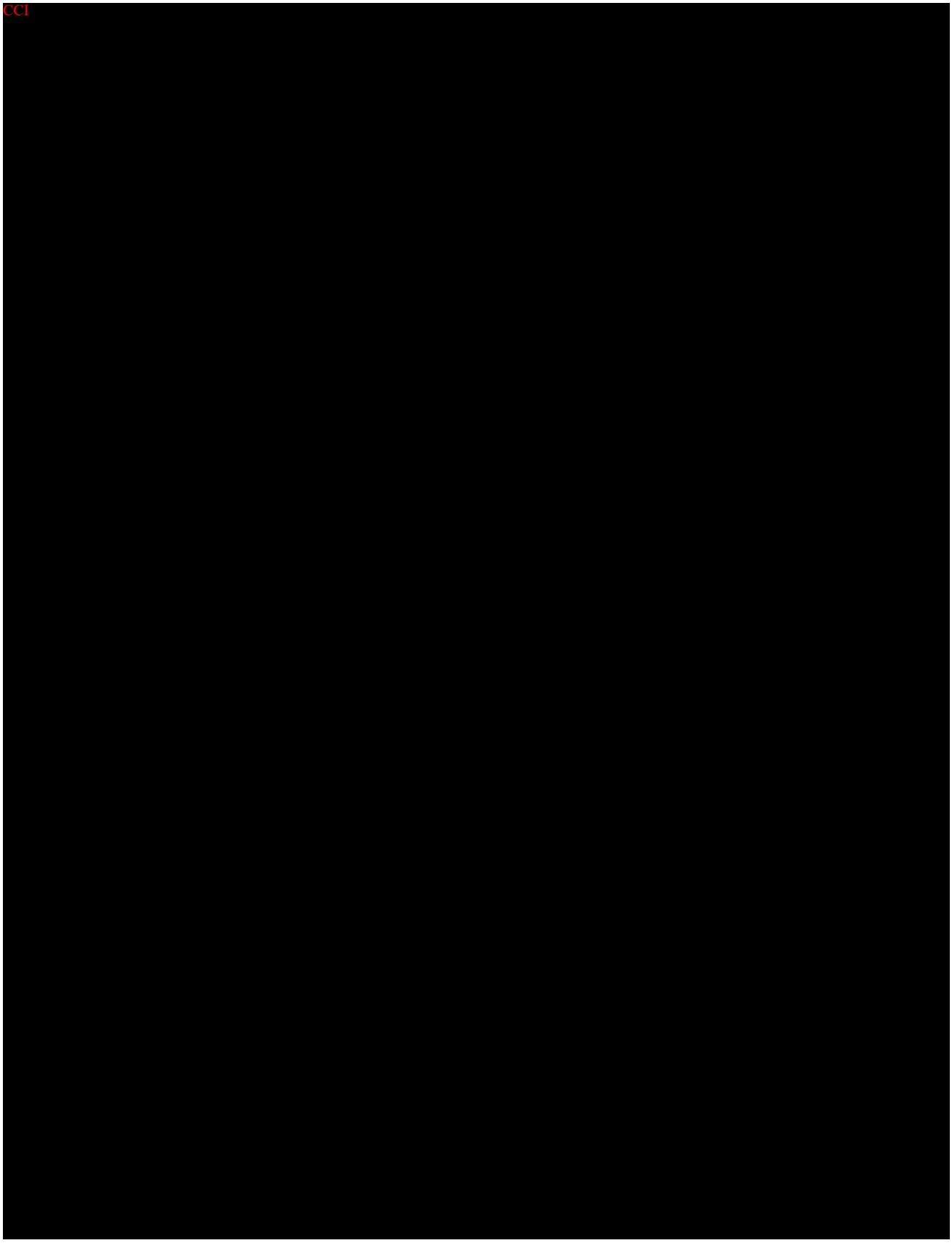

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4.6. Other Analyses

CCI

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CCI [redacted]

4.7. Interim Analyses

No formal interim analysis is planned for this study. CCI [redacted]

4.8. Changes to Protocol Defined Analyses

Changes from the originally planned statistical analysis specified in the protocol amendment 5 (Dated: 14-FEB-2023) are outlined below.

Protocol	Statistical Analysis Plan	Rationale for Changes
• No formal interim analysis will be done for this study.	CCI [redacted]	CCI [redacted]
• There is no protocol defined adverse events of special interest (AESI) for Dostarlimab.	• Analyses of AESIs are based on pre-defined MedDRA PTs.	CCI [redacted]

Protocol	Statistical Analysis Plan	Rationale for Changes
		CCI [redacted]
CCI [redacted]		

5. SAMPLE SIZE DETERMINATION

CCI [redacted]

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
CCI [redacted]	
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
BICR	Blinded Independent Central Review
BoR	Best Overall Response
CI	Confidence Interval
CCI [redacted]	
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
CCI [redacted]	
DCO	Data Cut-Off
DCR	Disease Control Rate
CCI [redacted]	

Abbreviation	Description
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Record Form
EGFR	Epidermal Growth Factor Receptor
CCI [redacted]	
GSK	GlaxoSmithKline
HR	Hazard Ratio
CCI [redacted]	
CCI [redacted]	
irAE	Immune Related Adverse Event
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Affairs
NE	Not Evaluable
NQ	Non-quantifiable
NSCLC	Non-Small Cell Lung Cancer
OPS	Output and Programming Specification
ORR	Objective Response Rate
OS	Overall Survival
PCI	Potential Clinical Importance
PD	Progressive Disease
CCI [redacted]	
PFS	Progression Free Survival
CCI [redacted]	
PP	Per-Protocol
PR	Partial Response
CCI [redacted]	
PT	Preferred Term
QTc	QT Interval Corrected for Heart Rate
Q3W	Every Three Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
CCI [redacted]	
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable Disease
SMQ	Standardized MedDRA Query
SOC	System Order Class

Abbreviation	Description
TEAE	Treatment Emergent Adverse Event
TOI	Term of Interest
CCI [redacted]	
ULN	Upper Limit of Normal

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies	Trademarks not owned by the GlaxoSmithKline Group of Companies
None	MedDRA

6.2. Appendix 2: Exclusions from Per Protocol Population

The per-protocol population include all participants in the ITT who do not have protocol deviations that may significantly impact the interpretation of efficacy results. CCI [redacted]

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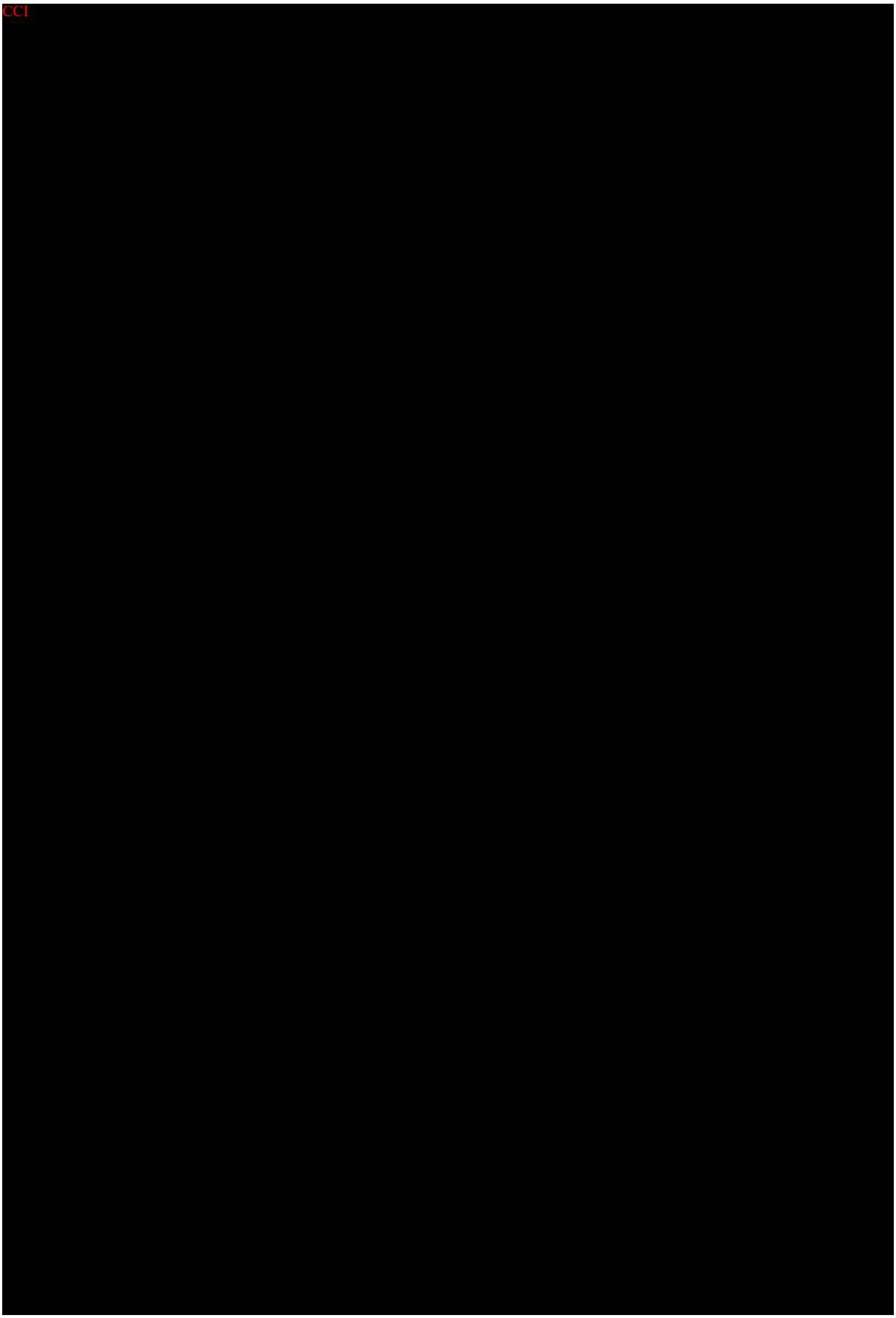

7. REFERENCES

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