TITLE PAGE

A RANDOMIZED, OPEN-LABEL PHASE 2/3 STUDY COMPARING COBOLIMAB + DOSTARLIMAB + DOCETAXEL TO DOSTARLIMAB + DOCETAXEL TO DOCETAXEL ALONE IN PARTICIPANTS WITH ADVANCED NON-SMALL CELL LUNG CANCER WHO HAVE PROGRESSED ON PRIOR ANTI-PD-(L)1 THERAPY AND CHEMOTHERAPY (COSTAR LUNG)

Brief Title:	Efficacy Comparison of Cobolimab + Dostarlimab + Docetaxel to Dostarlimab + Docetaxel to Docetaxel Alone in Participants with Advanced Non-Small Cell Lung Cancer Who Have Progressed on Prior Anti-PD-(L)1 Therapy and Chemotherapy
Protocol Number:	213410 /Amendment 8
Compound Name:	Cobolimab (GSK4069889A) Dostarlimab (GSK4057190A)
Study Phase:	Phase 2/3
Sponsor Name and Legal Registered Address:	GSK Research & Development Limited 79 New Oxford Street London WC1A 1DG UK
Sponsor Signatory Name:	Steven Hirschfeld MD, PhD Executive Medical Director, Oncology Clinical Development Lead

Regulatory Agency Identification Numbers:

Registry	ID
IND	145524
EU CT number	2023-507475-21-00

Approval Date: 04 Sep 2025

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PROTOCOL AMENDMENT 8 INVESTIGATOR AGREEMENT

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical and/or digital informed consent of the participant and/or the participant's LAR.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
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- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

Study identifier	213410
EU CT number	2023-507475-21-00
Approval date	04 Sep 2025
Brief Title	Efficacy Comparison of Cobolimab + Dostarlimab + Docetaxel to Dostarlimab + Docetaxel to Docetaxel Alone in Participants with Advanced Non-Small Cell Lung Cancer Who Have Progressed on Prior Anti-PD-(L)1 Therapy and Chemotherapy
Investigator name	_____
Signature	_____
Date of signature (DD Month YYYY)	_____
Name of Clinical Trial Leader, function and title	_____
Signature	_____
Date of signature (DD Month YYYY)	_____

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Table 1 Document History

Document	Date	Document Number
Amendment 08	04 Sep 2025	TMF-22602376
Amendment 07	20 December 2024	TMF-20391976
Amendment 06	24 July 2024	TMF-19423630
Amendment 05	11 August 2023	TMF-16223837
Amendment 04	06 October 2021	TMF-13956905
Amendment 03	22 December 2020	TMF-11698646
Amendment 02	21 October 2020	TMF-2115096
Amendment 01	16 October 2020	TMF-11715597
Original Protocol	24 September 2020	TMF-11715514

Amendment 08 (04 Sep 2025)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment

Amendment 08 is a global protocol amendment created to provide CCI [redacted]

CCI [redacted]

A table of key changes from Protocol Amendment 7 to Amendment 8 is shown below:

Summary of Changes for the Amendment

Table 2: Summary of Changes for Amendment 8

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
	CCI [redacted]	To reduce the burden on patients
Section 2.4.3 Section 4.4 Section 6.8 Section 8.5.1	CCI [redacted]	
Section 8.7 Section 8.8 Section 9.3.2	CCI [redacted]	To reduce patient burden CCI [redacted]

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

A Randomized, Open-Label Phase 2/3 Study Comparing Cobolimab + Dostarlimab + Docetaxel to Dostarlimab + Docetaxel to Docetaxel Alone In Participants with Advanced Non-Small Cell Lung Cancer Who Have Progressed on Prior Anti-PD-(L)1 Therapy and Chemotherapy (COSTAR Lung)

Brief Title

Efficacy Comparison of Cobolimab + Dostarlimab + Docetaxel to Dostarlimab + Docetaxel to Docetaxel Alone in Participants with Advanced Non-Small Cell Lung Cancer Who Have Progressed on Prior Anti-PD-(L)1 Therapy and Chemotherapy

Rationale

Although antibodies directed against immune checkpoints such as programmed cell death protein 1 (PD-1) and its ligand, programmed death-ligand 1 (PD-L1), have proven effective across multiple indications, there is still a large unmet medical need for patients who do not respond or who develop resistance during the course of treatment. There are several emerging hypotheses to explain the lack of response, including the overall presence and localization of immunosuppressive cells in the tumor, like regulatory T cells and myeloid-derived suppressor cells, as well as the up-regulation of additional T cell checkpoints on the tumor-infiltrating lymphocytes. T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) is a novel immune checkpoint initially identified on interferon-gamma (IFN-γ)-producing cluster of differentiation (CD)4^+ T-helper 1 and $CD8^+$ cytotoxic T (CD8 T) cells and has been implicated in the exhaustion of T cells. Up-regulation of TIM-3 expression on PD-1-positive tumor-infiltrating T cells in several cancers, such as non-small cell lung cancer (NSCLC), is associated with reduced proliferation and secretion of cytokines important for T cell-mediated antitumor activity. Blocking TIM-3 therefore has the potential to restore tumor recognition by T cells and increase tumor killing. Studies have demonstrated that blockade of TIM-3 enhances T cell function, as evidenced by increased T cell proliferation and release of IFN-γ and interleukin-2 (IL-2). Additionally, research has shown that TIM-3 blockade combined with paclitaxel promotes activation of dendritic cells, leading to increased CD8 T cell activation and antitumor activity (de Mingo Pulido, 2018).

Cobolimab (also known as TSR-022, GSK4069889A) is a novel, first-in-class anti-TIM-3 monoclonal antibody (mAb) that is in clinical development to treat solid tumors in combination with an anti-PD-1 antibody, dostarlimab (also known as TSR-042, GSK4057190A). The current hypothesis is that cobolimab in combination with dostarlimab will deepen responses to PD-1 blockade by reactivating antitumor immune pathways in tumors that are either refractory or have developed resistance after an initial response to an anti-PD-1 or anti-PD-L1 antibody.

Objectives and Endpoints

Objective	Endpoint
Primary	
To evaluate the efficacy of **cobolimab + dostarlimab + docetaxel** relative to **docetaxel alone** in participants with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy	• OS defined as survival from the date of randomization to the date of death by any cause
To evaluate the efficacy of **dostarlimab + docetaxel** relative to **docetaxel alone** in participants with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy	• OS defined as survival from the date of randomization to the date of death by any cause
Secondary	
To evaluate the efficacy of cobolimab + dostarlimab + docetaxel relative to dostarlimab + docetaxel	• OS defined as survival from the date of randomization to the date of death by any cause
To evaluate additional measures of clinical benefit for cobolimab + dostarlimab + docetaxel relative to docetaxel alone	• Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator assessment • PFS defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression based on RECIST v1.1 by Investigator assessment or death by any cause • DOR defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression based on RECIST v 1.1 by Investigator assessment or death, whichever occurs first • TTD in lung cancer defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13 • Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains

Objective	Endpoint
Secondary (continued)	
To evaluate additional measures of clinical benefit for dostarlimab + docetaxel relative to docetaxel alone	• Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator assessment • PFS defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression based on RECIST v1.1 by Investigator assessment or death by any cause • DOR defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression based on RECIST v 1.1 by Investigator assessment or death, whichever occurs first • TTD in lung cancer defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13 • Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains
To evaluate additional measures of clinical benefit for cobolimab + dostarlimab + docetaxel relative to dostarlimab + docetaxel	• Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator assessment • PFS defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression based on RECIST v1.1 by Investigator assessment or death by any cause • DOR defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression based on RECIST v 1.1 by Investigator assessment or death, whichever occurs first • TTD in lung cancer defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13 • Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains

Objective	Endpoint
To evaluate the safety and tolerability of cobolimab + dostarlimab + docetaxel and dostarlimab + docetaxel vs docetaxel alone	• The incidence of TEAEs, SAEs, imAEs, 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, and urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications will be collected.

Abbreviations: AE=adverse event; CR=complete response; DOR=duration of response; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item Lung Cancer Module; imAE=immune-mediated adverse event; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; PFS=progression-free survival; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TTD=time to deterioration.

Overall Design

This is a multicenter, parallel-group treatment, Phase 2/3 open-label, 3-arm study comparing cobolimab + dostarlimab + docetaxel to dostarlimab + docetaxel to docetaxel alone for efficacy in male and female participants aged 18 years and older with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy. Crossover between treatment arms will not be allowed in this study. The 3 treatment arms will be as follows:

1. **Arm A:** Cobolimab + dostarlimab + docetaxel
2. **Arm B:** Dostarlimab + docetaxel
3. **Arm C:** Docetaxel

Participants will be randomized into the 3 arms in a 2:2:1 ratio and stratified according to the following 3 factors:

1. Prior lines of therapy: 1 prior line vs 2 prior lines
2. PD-L1 status: tumor proportion score (TPS)≥50% vs TPS<50%
3. Histology: Squamous vs nonsquamous

The immunotherapy study treatments (cobolimab and dostarlimab in Arm A, dostarlimab only in Arm B) and the chemotherapy study treatment (docetaxel; all arms) will be administered every 3 weeks (Q3W). All therapies used in the study will be open-label (unblinded). Enrolled participants may continue study treatment until disease progression, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.



To enroll in the study, participants must have the following:

- Histologically or cytologically proven advanced or metastatic NSCLC, and only squamous or nonsquamous cell carcinoma
- Measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Received no more than 2 prior lines of therapy for advanced or metastatic disease, which must only include a platinum-based (eg, cisplatin, carboplatin) doublet chemotherapy regimen and an anti-PD-1 or anti-PD-L1 antibody (no other biologic alone or in combination; novel combinations are not allowed)
- Documented radiological disease progression on prior platinum-based chemotherapy and on prior anti-PD-1 or anti-PD-L1 therapy according to RECIST v1.1
- An archival tumor tissue biopsy (or a fresh tumor biopsy if archival is not available) of a primary or metastatic tumor; participants are also encouraged, but not required, to have a fresh tumor tissue biopsy of a primary or metastatic tumor prior to dosing (samples will be used to enable biomarker analysis)
- Documented PD-L1 status by the [redacted] If a prior PD-L1 result by 1 of these testing methods is not available at the time of Screening, the participant must submit an archival or fresh tumor tissue to be tested locally using 1 of these testing methods, or, if not available, submit for central testing by [redacted] Results are required for stratification and must be available prior to randomization.
- An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Participants who have or have had the following <u>will not be eligible</u> for the study:

- Prior treatment with an anti-PD-1, anti-PD-L1, or anti-programmed death-ligand 2 (anti-PD-L2) agent that resulted in permanent discontinuation due to an adverse event (AE)
- Prior treatment with an anti-TIM-3 agent or docetaxel

- Participant has a documented sensitizing epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), or c-ros oncogene 1 (ROS-1) mutation. Participants whose tumors have not been tested for these driver mutations and therefore who have unknown driver mutation status are not eligible. Participants with squamous histology do not need to be tested for these driver mutations.
- Radiological or clinical disease progression (ie, worsening performance status, clinical symptoms, and laboratory data) ≤8 weeks after initiation of prior anti-PD-1 or anti-PD-L1 antibody. The clinical disease progression should have been confirmed by a subsequent radiological scan.
- A known sensitivity to any of the study treatments, or components thereof

Brief Summary

The purpose of this study is to assess the efficacy and safety of cobolimab + dostarlimab in combination with chemotherapy (Arm A) to dostarlimab in combination with chemotherapy (Arm B) to chemotherapy alone (Arm C) in participants with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy. The study will determine whether the combination treatment arms prolong OS relative to docetaxel alone. Study details include the following:

- Treatment duration: Enrolled participants may continue study treatment until disease progression, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.
- Visit frequency: Weekly for Cycle 1 (cycles are 21 [±3] days), then Q3W thereafter; End-of-Treatment (EOT) Visit within 7 days after the last dose; Safety Follow-up Visit 30 (±7) days and 90 (±7) days after the last dose.
- Study duration: A participant's time on study will include Screening (28 days), the Treatment Period (treatment duration previously defined), and Follow-up (30- and 90-day safety assessments and continued follow-up every 90 days until death, withdrawal of consent, loss to follow-up, or the end of study data collection).

Number of Participants

Approximately 750 participants (250 participants in the Phase 2 portion and 500 participants in the Phase 3 portion) will be randomly assigned to study treatment.

Sample size determination details and analysis population definitions can be found in Section 9.2 and Section 9.3.1, respectively.

Treatment Groups and Duration

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 last dose/decision to discontinue treatment for any reason), a Safety Follow-up Visit 30 (±7) days and 90 (±7) days after the last dose of study treatment, and a Post-treatment Follow-up Period with assessments occurring every 90 (±14) days (from the 90-day Safety Follow-Up Visit) and continuing until death, withdrawal of consent, loss to follow-up, or the end of study data collection.

The treatments administered in this study include cobolimab, dostarlimab, and docetaxel.

Participants will be randomized 2:2:1 into the 3 study treatment arms (groups) and dosed with the treatments as follows, following any visit-mandated assessments:

- **Arm A:** Cobolimab + dostarlimab + docetaxel
  - 300 mg cobolimab via a 30 (-5 and +15)-minute intravenous (IV) infusion Q3W (administered first)
  - 500 mg dostarlimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered second)
  - 75 mg/m^2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles (administered third/last).
- **Arm B:** Dostarlimab + docetaxel
  - 500 mg dostarlimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered first)
  - 75 mg/m^2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles (administered second/last)
- **Arm C:** Docetaxel
  - 75 mg/m^2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles

Note: Docetaxel infusion time is based on the product label; institutional discretion on this parameter is not allowed. Docetaxel should be administered until disease progression or unacceptable toxicity (see Section 7.1) or according to local practice and the local approved product label.

All therapies used in the study will be open-label (unblinded). Enrolled participants may continue study treatment until disease progression, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.

Rules and procedures for dose adjustments and delays can be found in Section 6.4.

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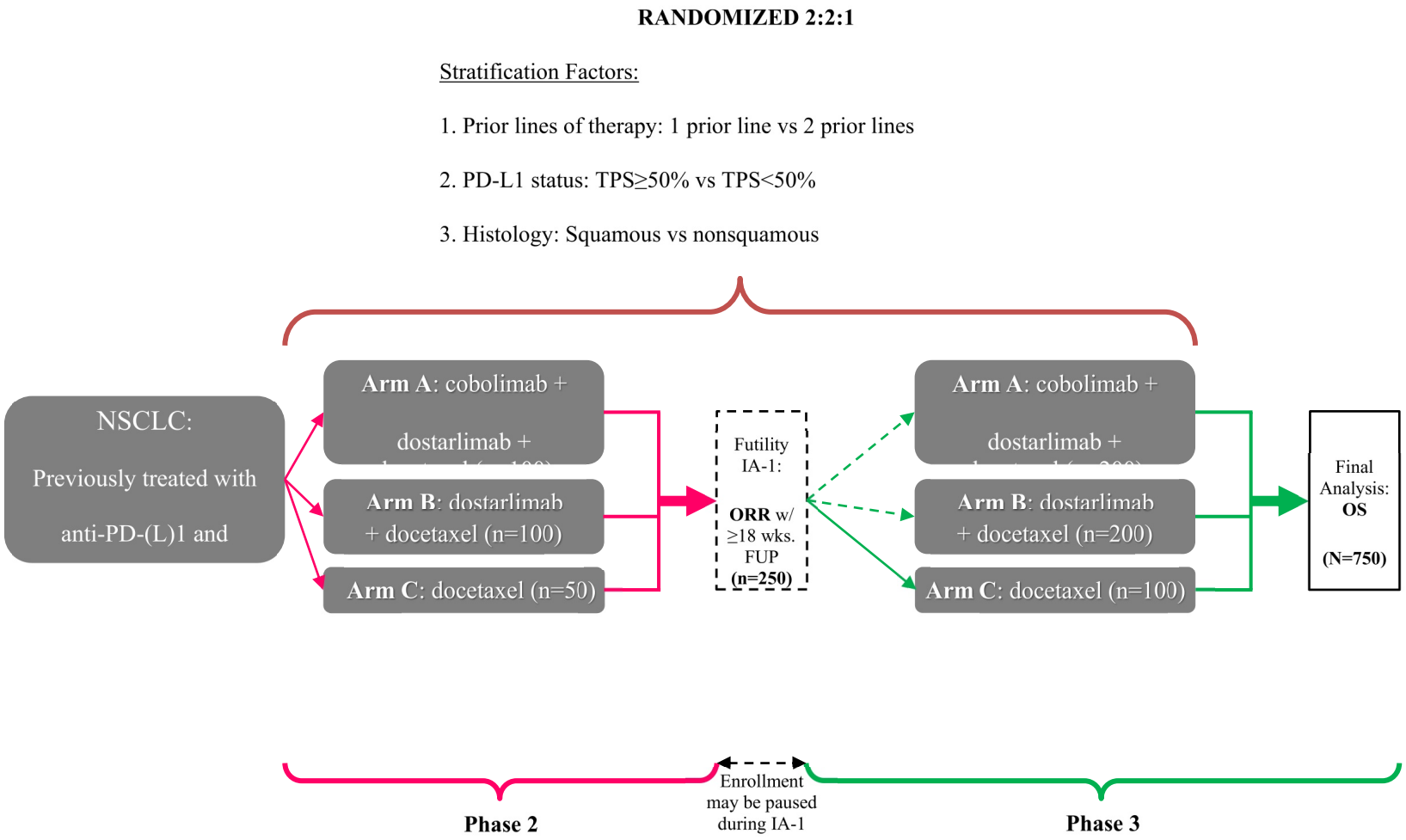
CCI

[redacted]

1.2. Schema

The schema for Study 213410 is presented in Figure 1.

Figure 1: Schema for Study 213410



Abbreviations: FUP=follow-up; IA=interim analysis; NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD 1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; TPS=tumor proportion score.

Note: Arm C represents current standard-of-care regimen and will continue through study completion regardless of the IA-1 result. The 750 total participants include the 250 participants from the futility analysis (IA-1).

1.3. Schedule of Activities

Schedules of study activities for Study 213410 are provided in Table 3. Each treatment cycle is 21 (±3) days. One month is defined as 4 weeks (28 days).

CCI



Table 3 Schedule of Activities for Study 213410

Visit: **Cycle:**	**Screening Period**	**Treatment Period***				**EOT (or ED) Visit[1]**	**Safety FUP Visit[1]**	**Post-treatment FUP Period[2]**	**Notes**
		C1			**C(n)**				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
SCREENING-ONLY ASSESSMENTS									
Informed consent	X								
Inclusion and exclusion criteria	X								Recheck clinical status before randomization and/or first dose.
Demographics	X								
Medical history	X								Including surgical and cancer (including genotyping) history.
Prior medications	X								
Current medical conditions	X								
PD-L1 status	X								Required for randomization; may require tumor tissue submission or collection. See Section 8.6.1.

Table 3: Schedule of Activities for Study 213410 (Continued)

Visit: Cycle:	Screening Period	Treatment Period*				EOT (or ED) Visit[1]	Safety FUP Visit	Post-treatment FUP Period[2]	Notes
		C1			C(n)				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
SCREENING-ONLY ASSESSMENTS (CONTINUED)									
Randomization		X							Randomization may occur up to 3 days before Day 1; the preference is to randomize within 24 hours before Day 1.
Optional blood sample for genetic testing	X								Sample is recommended to be collected at the first opportunity after participants have met all eligibility requirements and before C1D1 or dosing on C1D1.
LABORATORY ASSESSMENTS: Screening assessments completed within 72 hours of C1D1 do not need to be repeated. Safety laboratory assessments can be performed up to 72 hours prior to C1D1 and up to 24 hours (or 1 day) prior to dosing for subsequent cycles. All assessments are required to be performed, and results evaluated, prior to treatment administration. If participant is not dosed, this should not be considered a cycle and any assessment completed should be recorded as an unscheduled visit.									
HIV, hepatitis B, and hepatitis C screening	X								If a participant was tested within 3 months prior to the first dose of study treatment, testing at Screening is not required. See APPENDIX 4.

Table 3: Schedule of Activities for Study 213410 (Continued)

Visit: **Cycle:**	**Screening Period**	**Treatment Period***				**EOT (or ED) Visit[1]**	**Safety FUP Visit**	**Post-treatment FUP Period[2]**	**Notes**
		C1			**C(n)**				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
LABORATORY ASSESSMENTS (CONTINUED): Screening assessments completed within 72 hours of C1D1 do not need to be repeated. Safety laboratory assessments can be performed up to 72 hours prior to C1D1 and up to 24 hours (or 1 day) prior to dosing for subsequent cycles. All assessments are required to be performed, and results evaluated, prior to treatment administration. If participant is not dosed, this should not be considered a cycle and any assessment completed should be recorded as an unscheduled visit.									
Coagulation	X	X							Coagulation information will also be collected if required due to an AE and liver event. Please see approved units for INR/PT/aPTT in Table 17.
Thyroid panel	X	X			Q6W		X		
Serum chemistry	X	X			X	X	X		
Urinalysis	X	X			X	X	X		See APPENDIX 4 for analytes.
CBC with differential	X	X	X	X	X*	X	X		*Monitor CBC per local guidance while participant is receiving docetaxel. Local laboratories may be utilized for additional assessments; see Section 8.1.1 and Table 11.

Visit: Cycle:	Screening Period	Treatment Period*				EOT (or ED) Visit[1]	Safety FUP Visit	Post-treatment FUP Period[2]	Notes
		C1			C(n)				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
LABORATORY ASSESSMENTS (CONTINUED): Screening assessments completed within 72 hours of C1D1 do not need to be repeated. Safety laboratory assessments can be performed up to 72 hours prior to C1D1 and up to 24 hours (or 1 day) prior to dosing for subsequent cycles. All assessments are required to be performed, and results evaluated, prior to treatment administration. If participant is not dosed, this should not be considered a cycle and any assessment completed should be recorded as an unscheduled visit.									
Highly sensitive urine or serum pregnancy test (WOCBP only)	X	X			X	Monthly for at CCI [redacted] after the last dose of study treatment. (Note: Duration of contraceptive use after the last dose of docetaxel must be consistent with local requirements and the local approved product label; however, the minimum duration CCI [redacted] after the last dose of docetaxel.) (Local laboratories may be utilized for these additional assessments; see Section 8.1.1 and Table 11.)			A highly sensitive pregnancy test (urine or serum, as required by local regulations) is required within 72 hours before treatment administration. At Screening, if a urine test cannot be confirmed as negative (eg, ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. See Section 5.1, Section 8.4.6, and APPENDIX 4 and APPENDIX 6.

Table 3: Schedule of Activities for Study 213410 (Continued)

Visit: **Cycle:**	**Screening Period**	**Treatment Period***				**EOT (or ED) Visit[1]**	**Safety FUP Visit**	**Post-treatment FUP Period[2]**	**Notes**
		C1			**C(n)**				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
CLINICAL ASSESSMENTS (CONTINUED): Screening assessments completed within 72 hours of C1D1 do not need to be repeated. Assessments can be performed up to 72 hours prior to C1D1 and up to 24 hours prior to dosing for subsequent cycles. All assessments are required to be performed, and results evaluated, prior to treatment administration. If participant is not dosed, this should not be considered a cycle and any assessment completed should be recorded as an unscheduled visit.									
Full physical examination	X					X	X		
12-lead ECG	X	X							
Vital signs (including height* and weight)	X	X			X	X			*Height is measured at Screening only.
ECOG performance status	X	X			X	X			See APPENDIX 3.
Symptom-directed physical examination		X			X				

Visit: Cycle:	Screening Period	Treatment Period*				EOT (or ED) Visit[1]	Safety FUP Visit	Post-treatment FUP Period[2]	Notes
		C1			C(n)				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
CLINICAL ASSESSMENTS (CONTINUED): Screening assessments completed within 72 hours of C1D1 do not need to be repeated. Assessments can be performed up to 72 hours prior to C1D1 and up to 24 hours prior to dosing for subsequent cycles. All assessments are required to be performed, and results evaluated, prior to treatment administration. If participant is not dosed, this should not be considered a cycle and any assessment completed should be recorded as an unscheduled visit.									
Concomitant medication review		X	X	X	X	X	X		All concomitant medications will be collected from the start of study treatment until 90 days after the last dose of study treatment or until the participant starts alternate anticancer therapy, whichever occurs first.

Visit: **Cycle:**	**Screening Period**	**Treatment Period***				**EOT (or ED) Visit[1]**	**Safety FUP Visit**	**Post-treatment FUP Period[2]**	**Notes**
		C1			**C(n)**				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
AE/SAE monitoring and review	All AEs will be collected from the start of study treatment until 30 days after the last dose of study treatment or until the participant starts alternate anticancer therapy, whichever occurs first. SAEs will be collected from the start of study treatment until 90 days after the last dose of study treatment or until the participant starts alternate anticancer therapy, whichever occurs first. However, any SAE assessed as related to study participation or related to a GSK product will be recorded from the time a participant provides informed consent. CCI [redacted]								See Section 8.5.1

Table 3: Schedule of Activities for Study 213410 (Continued)

Visit: **Cycle:**	**Screening Period**	**Treatment Period***				**EOT (or ED) Visit[1]**	**Safety FUP Visit[1]**	**Post-treatment FUP Period[2]**	**Notes**
		C1			**C(n)**				
Day: **Procedure:**	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	* Treatment cycles are 21 (±3) days long. CCI [redacted] [2] For Post treatment FUP, please refer to Section 4.1
TREATMENT ADMINSTRATION									
Cobolimab administration (Arm A)		X			X				Dosing order: 1. Cobolimab (300 mg administered via a 30 [-5 and +15]-minute IV infusion Q3W; Arm A only)
Dostarlimab administration (Arms A and B)		X			X				

Docetaxel administration (All Arms: A, B, and C)		X			X		2. Dostarlimab (500 mg administered via a 30 [-5 and +15]-minute IV infusion Q3W; Arms A and B) 3. Docetaxel (75 mg/m2 administered via 60-minute IV infusion Q3W for a minimum of 4 cycles; all arms). Docetaxel infusion time is based on the product label; institutional discretion on this parameter is not allowed. Docetaxel should be administered until disease progression or unacceptable toxicity (see Section 7.1) or according to local practice and the local approved product label. For all participants, the post infusion observation period following the first and second cycles will be at least 4 hours after the last infusion. Participants will be monitored per institutional practice. Prophylactic G-CSF is strongly recommended to avoid neutropenia complications due to chemotherapy.

Table 3: Schedule of Activities for Study 213410 (Continued)

Visit: Cycle:	Screening Period	Treatment Period*				EOT (or ED) Visit[1]	Safety FUP Visit[1]	Post-treatment FUP Period[2]	Notes
		C1			C(n)				
Day: Procedure:	**Up to 28 days before D1**	**1**	**8**	**15**	**1**	**Within 7 days of last dose (or decision to discontinue)**	**30 (±7) days and 90 (±7) days after last dose**	**Every 90 (±14) days (from 90-day Safety FUP Visit)**	*Treatment cycles are 21 (±3) days long. [1] For modified follow up option, please see Section 7.2. [2] For Post treatment FUP, please refer to Section 4.1
FUP-ONLY ASSESSMENTS									
Anticancer therapies assessment							X	X	CCI

Abbreviations:-; AE=adverse event; aPTT=activated partial thromboplastin time; C=cycle; CBC=complete blood count; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; ED=early discontinuation/withdrawal;; EOT=End-of-Treatment; FUP=follow-up; GSK=GlaxoSmithKline;; ICF=informed consent form; INR=international normalized ratio; IV=intravenous;; n=number of subsequent cycle; PD-L1=programmed death-ligand 1;; PR=partial response; PT=prothrombin time; SAE=serious adverse event; WOCBP=women of childbearing potential.

2. INTRODUCTION

Cobolimab is a selective, humanized mAb of the IgG4/kappa isotype that binds to TIM-3 and can antagonize its inhibitory effects. In nonclinical studies, TIM-3 blockade enhances the antitumor activity of PD-1 in select murine models, and cobolimab specifically can increase T cell activation in multiple ex vivo human T cell assay systems. By combining cobolimab with anti-PD-1 in patients, immune cell activation may be enhanced resulting in improved and durable antitumor activity. As such, cobolimab is being developed as a combination immunotherapy for patients with advanced malignancies.

2.1. Study Rationale

Although antibodies directed against immune checkpoints such as PD-1 and its ligand, PD-L1, have proven effective across multiple indications, there is still a large unmet medical need for patients who do not respond or who develop resistance during the course of treatment. There are several emerging hypotheses to explain the lack of response, including the overall presence and localization of immunosuppressive cells in the tumor, like regulatory T cells and myeloid-derived suppressor cells, as well as the up-regulation of additional T cell checkpoints on the tumor-infiltrating lymphocytes. TIM-3 is a novel immune checkpoint initially identified on IFN-γ-producing $CD4^+$ T-helper 1 and CD8 T cells and has been implicated in the exhaustion of T cells. Up-regulation of TIM-3 expression on PD-1-positive tumor-infiltrating T cells in several cancers, such as NSCLC, is associated with reduced proliferation and secretion of cytokines important for T cell-mediated antitumor activity. Blocking TIM-3 therefore has the potential to restore tumor recognition by T cells and increase tumor killing. Studies have demonstrated that blockade of TIM-3 enhances T cell function, as evidenced by increased T cell proliferation and release of IFN-γ and IL-2. Additionally, research has shown that TIM-3 blockade combined with paclitaxel promotes activation of dendritic cells, leading to increased CD8 T cell activation and antitumor activity (de Mingo Pulido, 2018).

Cobolimab is a novel, first-in-class anti-TIM-3 mAb that is in clinical development to treat solid tumors in combination with an anti-PD-1 antibody, dostarlimab. The current hypothesis is that cobolimab in combination with dostarlimab will deepen responses to PD-1 blockade by reactivating antitumor immune pathways in tumors that are either refractory or have developed resistance after an initial response to an anti-PD-1 or anti-PD-L1 antibody.

2.2. Background

In this study, cobolimab in combination with dostarlimab and docetaxel (taxane chemotherapy) is being investigated to treat advanced NSCLC, as this patient population represents a high unmet medical need. This study and select cohorts of the ongoing Phase 1 Study 4020-01-001 (AMBER; GSK Study 213348) and the Phase 1 Study 204691 (INDUCE-1) represent the only studies of cobolimab in NSCLC by the Sponsor at this time.

In the AMBER expansion cohorts B2 (dostarlimab 500 mg + cobolimab 100 mg), B3 (dostarlimab 500 mg + cobolimab 300 mg) and B4 (dostarlimab 500 mg + cobolimab 900 mg), eligibility requirements include histologically proven advanced or metastatic NSCLC (measurable by computed tomography [CT] or magnetic resonance imaging [MRI] per RECIST v1.1) that progressed following treatment with an anti-PD-1 or anti-PD-L1 antibody and no limit on prior lines of anticancer therapy for advanced or metastatic disease.

Eighty-four participants were enrolled in Cohorts B2, B3, and B4 as of 01 December 2019. There was a total of 10 participants with a partial response (PR) across all 3 cohorts, 6 of which were confirmed by RECIST v1.1. Signs of combination activity were greater in Cohort B3 (300 mg cobolimab) compared to Cohort B2 (100 mg cobolimab) or Cohort B4 (900 mg cobolimab); there were 4 confirmed partial responses (cPRs) by RECIST v1.1 in Cohort B3 compared to 1 cPR each in Cohorts B2 and B4. Across all cohorts, durable responses and stable disease (SD) were observed following treatment with cobolimab + dostarlimab, with 5 participants beyond a year of treatment. As of the data cut, 3 participants remained on treatment.

2.3. Lung Cancer

Lung cancer is the most common cause of cancer mortality globally and the second most common cancer in both men and women. About 13% of all new cancers in the United States (US) are lung cancer (Howlader, 2018). Most recent lung and bronchus cancer incidence rates in the US from the Surveillance, Epidemiology, and End Results program estimate an incidence rate of 50.0 per 100,000 per year from 2016-2020 data (NCI SEER Lung Cancer, 2020). The 2 major forms of lung cancer are NSCLC and small cell lung cancer. NSCLC is a heterogeneous disease that consists of adenocarcinoma, large cell carcinoma, and squamous cell carcinoma, and comprises approximately 84% of all lung cancers (Herbst, 2008). The average age of diagnosis is approximately 70 years old. Despite advances in early detection and standard treatment, NSCLC is often diagnosed at an advanced stage, has poor prognosis, and is the leading cause of cancer deaths worldwide (Santarpia, 2017). In the US, the 5 year relative OS rate of all stages of NSCLC is approximately 25.4%, with advanced patients (Stage IV) having a 5 year OS rate of 8.2% (NCI SEER Lung Cancer, 2020).

2.3.1. Immuno-Oncology Therapy – PD-1 and TIM-3 Checkpoints

PD-1 and PD-L1 represent an immune inhibitory mechanism employed by tumors to subvert the immune response and disruption of this axis enhanced the lysis of tumor cells by T cells. Multiple clinical studies in tumors such as melanoma, renal cell carcinoma, and NSCLC have yielded positive data using anti-PD-1 or anti-PD-L1 targeted therapies.

In addition to PD-1, there are other immune proteins that have been shown to mediate T cell exhaustion, including TIM-3. TIM-3 was initially identified as a protein selectively expressed on IFN-γ-producing $CD4^+$ T helper 1 cells and CD8 T cells (Monney, 2002). Early studies demonstrated blockade of TIM-3 enhanced T cell function, as evidenced by increased T helper 1 cell proliferation and release of IFN-γ and IL-2 (Monney, 2002). A role for TIM-3 in mediating T cell exhaustion in cancer has been suggested in multiple

nonclinical murine models showing expression of TIM-3 and PD-1 on tumor-infiltrating lymphocytes (TILs) (Dardalhon, 2010; Ngiow, 2011; Sakuishi, 2010). The therapeutic efficacy of targeting these proteins demonstrated limited tumor control with TIM-3 or PD-1 blockade alone but enhanced immune-mediated control of tumor growth with concurrent TIM-3 and PD-1 blockade. These data demonstrate the expression of TIM-3 and PD-1 on TILs and implicated TIM-3 and PD-1 in limiting T cell effector function in the tumor microenvironment.

Similar to the effects observed in murine models, TIM-3 expression on TILs in human tumors has also been shown to mediate immunosuppression. A wide variety of tumor types are infiltrated by CD8 T cells and these CD8 T cells express TIM-3 and PD-1 as well as lymphocyte-activation gene 3 (LAG-3) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) (Baitsch, 2012; Gros, 2014; Thommen, 2015). Intriguingly, the presence of TIM-3^+ T cells was increased in patients with NSCLC with more advanced disease. Additional studies have reported the expression of TIM-3 on tumor-infiltrating regulatory T cells that correlates with enhanced immunosuppressive properties of these cells in an ex vivo assay (Jie, 2013). In patients with melanoma, characterization of TIM-3 expression on CD8 T cells specific for a tumor antigen revealed that coexpression of TIM-3 and PD-1 marks TILs with the lowest proliferative potential that also fail to produce IL-2, tumor necrosis factor alpha (TNFα), and IFN-γ (Fourcade, 2010). The function of CD8 T cells from these patients that coexpress TIM-3 and PD-1 demonstrate suppressed secretion of IFN-γ, TNFα, and IL-2 following ex vivo stimulation that can be improved via blockade of both TIM-3 and PD-1 (Fourcade, 2010). In addition to a role on CD8 T cells, regulatory T cells that suppress T cell function can express TIM-3 and are enriched within the tumor microenvironment in human tumors and murine models. These TIM-3^+ regulatory T cells exhibit superior suppressive capability relative to TIM-3^- regulatory T cells resulting in limited CD8 T cell-mediated antitumor immunity (Jie, 2013; Sakuishi, 2013). Thus, the presence and function of TIM-3-expressing T cells in the tumor microenvironment in humans largely reflect the data generated in murine models and support the exploration of TIM-3 blockade as a strategy to enhance antitumor immunity.

2.3.2. Current Treatment Options for Patients with NSCLC who Progress on Anti-PD-1 or Anti-PD-L1 Therapy

The introduction of anti-PD-1 and anti-PD-L1 therapy in the first-line setting has improved outcomes for patients with NSCLC without an aberration in a driver oncogene. However, many patients with NSCLC do not respond to first-line anti-PD-1 or anti-PD-L1 therapy (45% ORR in pembrolizumab monotherapy patients with tumor proportion score [TPS] ≥50%; 48% ORR in pembrolizumab + chemotherapy patients with nonsquamous NSCLC), and most of those who do respond will typically progress within a year. For patients who progress on an anti-PD-1 or anti-PD-L1 antibody and platinum-based chemotherapy, there are no drugs approved, nor is there an established standard of care in this setting. Drugs approved for second-line treatment of NSCLC following a platinum-based regimen (docetaxel, ramucirumab in combination with docetaxel, or pemetrexed [nonsquamous NSCLC only]) provide limited benefits with response rates ranging from 5.5% to 23%, progression-free survival (PFS) of 3 to 4.5 months (Barton, 2011; CYRAMZA Prescribing Information, 2018; Docetaxel Prescribing Information, 2019), and OS ranging from 5.7 to 10.5 months

(Borghaei, 2015; CYRAMZA Prescribing Information, 2018; Docetaxel Prescribing Information, 2019; Garon, 2014; KEYTRUDA Prescribing Information, 2020).

2.3.3. Rationale for Studying Immuno-Oncology Therapy Combinations and Immuno-Oncology Therapies in Combination with Chemotherapy in NSCLC

The lack of benefit of current treatment options to patients with NSCLC may be due to additional immunosuppressive mechanisms, such as those mediated by TIM-3. Early combination treatment enables the assessment of TIM-3 and PD-1 blockade to address de novo resistance to anti-PD-1 blockade while preventing 1 of the mechanisms that may result in resistance to anti-PD-1 monotherapy.

There are several lines of evidence that suggest the activity of anti-TIM-3 will be optimized in the setting of concurrent treatment with anti-PD-1. First, the blockade of TIM-3 may result in an increase in IFN-γ, and IFN-γ induces PD-L1 expression (Dong, 1999; Freeman, 2000). Second, the majority of TIM-3-expressing cells also express PD-1 (Baitsch, 2012; Gros, 2014; Thommen, 2015). Third, treatment with anti-PD-1 has been shown to increase TIM-3 expression (Koyama, 2016; Shayan, 2015). Thus, multiple lines of evidence suggest that the combination of anti-TIM-3 and anti-PD-1 will provide the greatest opportunity to observe clinical activity. Additionally, no data suggest TIM-3 blockade has a detrimental effect on anti-PD-1 treatment.

Docetaxel, a commercially available chemotherapeutic agent of the taxane chemotherapy drug class, also presents the opportunity to enhance the effects of an anti-TIM-3 agent like cobolimab. TIM-3 blockade in combination with PD-1 blockade results in robust invigoration of T cell responses (Anderson, 2014). In addition to its T cell intrinsic role, TIM-3 has been shown to negatively regulate dendritic cell function in the context of immunogenic cell death induced by taxanes. Nonclinical evidence demonstrates superior antitumor activity of the combination of paclitaxel and anti-TIM-3, compared to paclitaxel alone. When combined with taxane, TIM-3 blockade enhances the Type 1 interferon response in intratumoral dendritic cells, resulting in increased production of chemokines CXCL9/CXCL10, ultimately driving improved effector CD8 T cell function and increased antitumor efficacy (de Mingo Pulido, 2018).

To summarize, the possibility of improving the clinical benefit of immunotherapies for patients with advanced/metastatic NSCLC who have limited treatment options presents an opportunity to improve clinical outcomes. Given the clinical activity of antibodies targeting the PD-1 axis in a broad range of solid tumors, patients with NSCLC are expected to derive clinical benefit with the addition of TIM-3 blockade and taxane chemotherapy.

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For further details on the observed nonclinical and clinical safety and efficacy of cobolimab and dostarlimab, refer to the respective IBs. Note that dostarlimab (JEMPERLI) is now an approved and marketed product for the treatment of certain cancers; refer to the prescribing information for further information. For more information about docetaxel, refer to the manufacturer's prescribing information.

2.4. Benefit/Risk Assessment

This section outlines the risk assessment and mitigation strategy for the study treatments in this protocol. More detailed information about the known and expected benefits and risks and reasonably expected AEs of cobolimab and dostarlimab may be found in the respective IBs. Details regarding the known and expected benefits and risks of docetaxel can be found in the local approved product label.

2.4.1. Risk Assessment

The risk assessment for the study treatments in this protocol is provided in Table 4.

Table 4: Risk Assessment for Study 213410

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Table 4: Risk Assessment for Study 213410 (Continued)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Docetaxel		
Deaths due to toxicity/increased risk of mortality	Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m2 (Docetaxel Prescribing Information, 2019).	Participants who have received prior docetaxel are excluded. Liver function tests are required before each cycle.
Hepatotoxicity	Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of Grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and death due to toxicity. Patients with isolated elevations of transaminase >1.5×ULN also had a higher rate of Grade 4 febrile neutropenia but did not have an increased incidence of death due to toxicity. Bilirubin, AST or ALT, and alkaline phosphatase values should be obtained prior to each cycle of docetaxel therapy (Docetaxel Prescribing Information, 2019).	Relevant entry criteria, schedule for frequent monitoring, and dose modification guidance are outlined in the protocol. Liver function tests are required before each cycle.
Neutropenia	Neutropenia (<2,000 neutrophils/mm3) occurs in virtually all patients given 60 mg/m2 to 100 mg/m2 of docetaxel, and Grade 4 neutropenia (<500 cells/mm3) occurs in 85% of patients given 100 mg/m2 and 75% of patients given 60 mg/m2.	Relevant entry criteria, schedule for frequent monitoring, and dose modification guidance are outlined in the protocol.

Table 4: Risk Assessment for Study 213410 (Continued)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Docetaxel (continued)		
Hypersensitivity reactions	Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or, very rarely, fatal anaphylaxis have been reported in patients who received a 3-day dexamethasone premedication ((Docetaxel Prescribing Information, 2019).	Participants with a history of severe hypersensitivity reactions to drugs formulated with polysorbate 80 are excluded. Severe reactions require immediate discontinuation of docetaxel and administration of appropriate therapy, as outlined in the approved labels.
Fluid retention	Severe fluid retention occurred in 6.5% (6 of 92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by 1 or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites) (Docetaxel Prescribing Information, 2019).	Premedication regimen of dexamethasone, as outlined in the protocol.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; imAE=immune-mediated adverse event; IRR=infusion-related reaction; mAb=monoclonal antibody; NSCLC=non-small cell lung cancer; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; ULN=upper limit of normal.

2.4.2. Benefit Assessment

Research has shown that TIM-3 blockade combined with paclitaxel promotes activation of dendritic cells, leading to increased CD8 T cell activation and antitumor activity (de Mingo Pulido, 2018). CCI

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2.4.3. Overall Benefit/Risk Conclusion

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3. OBJECTIVES AND ENDPOINTS

Table 5: Objectives and Endpoints for Study 213410

Objective	Endpoint
Primary	
To evaluate the efficacy of **cobolimab + dostarlimab + docetaxel** relative to **docetaxel alone** in participants with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy	• OS defined as survival from the date of randomization to the date of death by any cause
To evaluate the efficacy of **dostarlimab + docetaxel** relative to **docetaxel alone** in participants with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy	• OS defined as survival from the date of randomization to the date of death by any cause
• **Secondary**	
To evaluate the efficacy of cobolimab + dostarlimab + docetaxel relative to dostarlimab + docetaxel	• OS defined as survival from the date of randomization to the date of death by any cause
To evaluate additional measures of clinical benefit for **cobolimab + dostarlimab + docetaxel** relative to **docetaxel alone**	• Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator assessment • PFS defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression based on RECIST v1.1 by Investigator assessment or death by any cause • DOR defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression based on RECIST v 1.1 by Investigator assessment or death, whichever occurs first • TTD in lung cancer defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13 • Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains

Objective	Endpoint
To evaluate additional measures of clinical benefit for **dostarlimab + docetaxel** relative to **docetaxel alone**	• Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator assessment • PFS defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression based on RECIST v1.1 by Investigator assessment or death by any cause • DOR defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression based on RECIST v 1.1 by Investigator assessment or death, whichever occurs first • TTD in lung cancer is defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13 • Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains
To evaluate additional measures of clinical benefit for **cobolimab + dostarlimab + docetaxel** relative to **dostarlimab + docetaxel**	• Confirmed ORR defined as the proportion of participants who have achieved confirmed CR or confirmed PR, evaluated using RECIST v1.1 based on Investigator assessment • PFS defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression based on RECIST v1.1 by Investigator assessment or death by any cause • DOR defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression based on RECIST v 1.1 by Investigator assessment or death, whichever occurs first • TTD in lung cancer defined as time from randomization to meaningful deterioration on a composite endpoint of dyspnea, chest pain, and cough, from the EORTC-QLQ-LC13 • Change from baseline as assessed by the EORTC-QLQ-C30 and the EORTC-QLQ-LC13 domains
To evaluate the safety and tolerability of **cobolimab + dostarlimab + docetaxel** and **dostarlimab + docetaxel** vs **docetaxel** alone	• The incidence of TEAEs, SAEs, imAEs, 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, and urinalysis), vital signs, ECOG performance status, ECG parameters, physical examinations, and usage of concomitant medications will be collected.

Objective	Endpoint
Exploratory	
CCI [redacted]	

Abbreviations: ADA=antidrug antibody; AE=adverse event; CD=cluster of differentiation; CD8 T=CD8+ cytotoxic T (cells); CR=complete response; ctDNA=circulating tumor DNA; DOR=duration of response; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30-item Core Module; EORTC-QLQ-LC13=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 13-item Lung Cancer Module; CCI [redacted] iCPD=iRECIST-confirmed progressive disease; imAE=immune-mediated adverse event; iRECIST=modified Response Evaluation Criteria in Solid Tumors NAb=neutralizing antibody; NSCLC=non-small cell lung cancer; NSCLC-SAQ=Non-Small Cell Lung Cancer-Symptom Assessment Questionnaire; ORR=objective response rate; OS=overall survival; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; PFS=progression-free survival; CCI [redacted] PK=pharmacokinetics; PR=partial response; PRO=patient-reported outcome; PRO-CTCAE=Patient-reported Outcomes Version of the Common Term Criteria for Adverse Events; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; TEAE=treatment-emergent adverse events; TIM-3=T-cell immunoglobulin and mucin-domain containing-3; TTD=time to deterioration.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, parallel-group treatment, Phase 2/3 open-label, 3-arm study comparing cobolimab + dostarlimab + docetaxel to dostarlimab + docetaxel to docetaxel alone for efficacy in male and female participants aged 18 years and older with advanced NSCLC who have progressed on prior anti-PD-1 or anti-PD-L1 therapy and chemotherapy. Crossover between treatment arms will not be allowed in this study. The 3 treatment arms will be as follows:

1. **Arm A:** Cobolimab + dostarlimab + docetaxel
2. **Arm B:** Dostarlimab + docetaxel
3. **Arm C:** Docetaxel

There will be an IA, a final analysis and an end of main study (EoMS) analysis. The IA-1 will be a futility analysis to assess ORR across the 3 arms and will be conducted after 250 participants are enrolled in total (100 participants each in Arms A and B and 50 participants in Arm C) and have been followed for at least 18 weeks, have withdrawn from the study, or have died. The Sponsor plans to pause enrollment during IA-1 while the futility analysis occurs; the Sponsor will communicate relevant details such as the anticipated duration of the pause, the outcome of the futility analysis (eg, all 3 study arms continue, 1 arm dropped, or study terminated), and information on when enrollment will resume to the sites and Health Authorities as applicable. The period before IA-1 will be considered the Phase 2 portion of the study and the period after IA-1 will be considered the Phase 3 portion of the study.

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 last dose/decision to discontinue treatment for any reason), a Safety Follow-up Visit at 30 (±7) days and at 90 (±7) days after the last dose of study treatment, and a Post-treatment Follow-up Period with assessments occurring every 90 (±14) days (from the 90-day Safety Follow-Up Visit) and continuing until death, withdrawal of consent, loss to follow-up, or the end of study data collection.

To be eligible for the study, participants must have documented PD-L1 status by the [redacted] If a prior PD-L1 result by 1 of these testing methods is not available at the time of Screening, the participant must submit archival or fresh tumor tissue to be tested locally using 1 of these testing methods, or, if not available, submit for central testing by [redacted]. Results of baseline PD-L1 status assessment are required for stratification and must be available prior to randomization. Participants who do not have documented PD-L1 status by the [redacted]

Following informed consent and completion of all Screening assessments, all participants who meet the eligibility criteria will be randomized 2:2:1 to receive cobolimab + dostarlimab + docetaxel, dostarlimab + docetaxel, or docetaxel alone, respectively. Randomization will be programmed by computer and all study treatments will be dispensed in an unblinded manner (open-label). The dosing regimen is described in Section 6.1. Randomization will be stratified by the following 3 factors:

1. Prior lines of therapy: 1 prior line vs 2 prior lines
2. PD-L1 status: TPS ≥50% vs TPS <50%
3. Histology: Squamous vs nonsquamous

Participants are required to submit to the central laboratory an archival formalin-fixed paraffin-embedded (FFPE) tumor tissue specimen (and accompanying pathology report) that was collected on or after diagnosis of metastatic disease from location(s) not irradiated prior to biopsy. Both tissue block and freshly cut slides are acceptable. If archival tissue is not available, the participant must undergo a fresh tissue biopsy prior to study entry.

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[redacted]

Number of Participants

Approximately 750 participants (250 participants in the Phase 2 portion and 500 participants in the Phase 3 portion) will be randomly assigned to study treatment.

Treatment Groups and Duration

The treatments administered in this study include cobolimab, dostarlimab, and docetaxel. All treatments used in the study will be open-label (unblinded). Enrolled participants may continue study treatment until disease progression, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.

- Cobolimab is a humanized monoclonal IgG4 antibody and will be supplied as a solution in vials containing CCI [redacted]
- Dostarlimab is an IgG4 antibody and will be supplied as a solution in vials containing CCI [redacted]
- Docetaxel is a chemotherapeutic agent. Docetaxel for injection may be supplied by the Sponsor or may be obtained locally as a commercially available dosage formulation with reimbursement by the Sponsor.

Participants will be randomized 2:2:1 into the 3 study treatment arms (groups) and dosed with the previously listed treatments as follows, following any visit-mandated assessments:

- **Arm A:** Cobolimab + dostarlimab + docetaxel
  - 300 mg cobolimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered first)
  - 500 mg dostarlimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered second)

  - 75 mg/m^2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles (administered third/last)

- **Arm B:** Dostarlimab + docetaxel
  - 500 mg dostarlimab via a 30 (-5 and +15)-minute IV infusion Q3W (administered first)
  - 75 mg/m^2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles (administered second/last)
- **Arm C:** Docetaxel
  - 75 mg/m^2 docetaxel via a 60-minute IV infusion Q3W for a minimum of 4 cycles

Note: Docetaxel infusion time is based on the product label; institutional discretion on this parameter is not allowed. CCI [redacted]

CCI [redacted]

4.2. Scientific Rationale for Study Design

Although there are no clinical efficacy data for cobolimab and dostarlimab in combination with docetaxel, nonclinical evidence shows improved antitumor efficacy of the triplet compared to chemotherapy alone in a NSCLC humanized tumor model. TIM-3 blockade in combination with PD-1 blockade results in robust invigoration of T cell responses (Anderson, 2014). In addition to its T cell intrinsic role, TIM-3 has been shown to negatively regulate dendritic cell function in the context of immunogenic cell death induced by taxanes. Nonclinical evidence demonstrates superior antitumor activity of the combination of paclitaxel and anti-TIM-3, compared to paclitaxel alone. When combined with taxane, TIM-3 blockade enhances the Type 1 interferon response in intratumoral dendritic cells, resulting in increased production of chemokines CXCL9/CXCL10, ultimately driving improved effector CD8 T cell function and increased antitumor efficacy (de Mingo Pulido, 2018).

Additionally, a recent Phase 2 clinical study of another anti-PD-1 antibody, pembrolizumab, in combination with docetaxel in immuno-oncology (IO)-naïve participants with NSCLC suggests potential value of immunotherapies in combination with docetaxel in patients with NSCLC (Arrieta, 2019). In the Phase 2, study 40 participants received pembrolizumab (200 mg) + docetaxel (75 mg/m^2) and 38 participants received docetaxel alone (75 mg/m^2); a statistically significant difference in terms of ORR (42.5% vs 15.8%; odds ratio: 3.9 [95% confidence interval (CI): 1.34 to 11.5]; p=0.01) was shown in participants receiving pembrolizumab + docetaxel compared with docetaxel alone. Furthermore, participants receiving pembrolizumab + docetaxel had a significantly longer PFS compared with those receiving docetaxel monotherapy (9.5 months [95% CI: 4.2 months to not reported] vs 3.9 months [95% CI: 3.2 to 5.7 months]; HR: 0.24 [95% CI: 0.13 to 0.46]; p<0.001). The most common AEs were fatigue (65% vs 63.2%), anemia (65% vs 50%) and nausea (52.5% vs 47.4%) in the pembrolizumab + docetaxel and docetaxel monotherapy arms, respectively. A total of 22.5% vs 5.3% of participants experienced an immune-mediated adverse event (imAE)of any-grade pneumonitis in the pembrolizumab + docetaxel and docetaxel monotherapy arms, respectively, while 27.5% vs 16% experienced any-grade hypothyroidism. In terms of non-imAEs, 0% vs 18.4% of participants experienced hypomagnesaemia in the pembrolizumab + docetaxel and docetaxel monotherapy arms, respectively, while 20% vs 0% experienced lymphopenia.

Due to the expectation of higher efficacy in the combination treatment arms compared to docetaxel alone, participants will be randomized to treatment arms in a 2:2:1 ratio.

4.2.1. Participant input into design

During the design of the study, input and suggestions from patients with cancer were taken into consideration.

4.3. Justification for Dose

As determined in the Phase 1 Study 4020-01-001 (AMBER; GSK Study 213348), the recommended clinical dose of cobolimab deemed safe and demonstrating adequate receptor engagement of TIM-3 is 300 mg Q3W. CCI

CCI

As determined in the Phase 1/2 Study 4010-01-001 (GARNET; GSK Study 213346), the recommended clinical dose of dostarlimab deemed safe and effective is 500 mg Q3W for 4 cycles, followed by 1,000 mg Q6W. To allow for consistency during the Treatment Period of this study, dostarlimab dosing will remain at 500 mg Q3W dosing for all cycles.

The standard approved dose of docetaxel for the treatment of NSCLC (75 mg/m^2 Q3W) will be used in all treatment arms of the study. CCI

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Additional dose justification information for cobolimab and dostarlimab can be found in the respective IBs.

4.4. Participant and Study Completion

A participant will be considered to have completed the study if the participant dies during the Treatment Period or Follow-up Period or if the study is closed/terminated. The cause of death should be documented in the electronic case report form (eCRF). 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, or at the Investigator's discretion is no longer being followed.

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5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant is ≥18 years old, is able to understand the study procedures, and agrees to participate in the study by providing written informed consent (as described in APPENDIX 5), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

   Note: Participants in Korea are eligible if they are 19 years or older at the time consent is obtained.

2. Participant has histologically or cytologically proven advanced or metastatic NSCLC, and only squamous or nonsquamous cell carcinoma.
3. Participant has received no more than 2 prior lines of therapy for advanced or metastatic disease, which must only include a platinum-based (e.g., cisplatin, carboplatin) doublet chemotherapy regimen and an anti-PD-1 or anti-PD-L1 antibody (no other biologic alone or in combination; novel combinations are not allowed).

   CCI [redacted]

   Two components of treatment must have been received in the same line or as separate lines of therapy as follows:

   - A maximum of 1 line of therapy containing a platinum-based chemotherapy in the metastatic setting

   and

   - A maximum of 1 line of therapy containing an anti-PD-1 or anti-PD-L1 antibody

   Note the following:

CCI [redacted]

CCI [redacted]

4. Participant has measurable disease, that is, presenting with at least 1 measurable lesion per RECIST v1.1 as determined by the local site Investigator/radiology assessment. Target lesions situated in a previously irradiated area are considered measurable if disease progression has been demonstrated in such lesions and if there are other target lesions. If there is only 1 target lesion that was previously irradiated, the participant is not eligible. See APPENDIX 1 for the definition of a measurable lesion.
5. Participant has documented radiological disease progression on prior platinum-based chemotherapy and on prior anti-PD-1 or anti-PD-L1 therapy according to RECIST v1.1.
6. Participant agrees to submit an archival FFPE tumor tissue specimen that was collected on or after diagnosis of metastatic disease from location(s) not irradiated prior to biopsy. Both tissue block and freshly cut slides are acceptable. If archival tissue is not available, the participant must undergo biopsy prior to study entry. See the Study Reference Manual for further details.

CCI [redacted]

7. Participant has documented PD-L1 status by the CCI [redacted]
CCI [redacted]
CCI [redacted] If a prior PD-L1 result by 1 of these testing methods is not available at the time of Screening, the participant must submit archival or fresh tumor tissue to be tested locally using 1 of these testing methods, or, if not available, submit for central testing by CCI [redacted] Results are required for stratification and must be available prior to randomization.

a. For participants requiring PD-L1 testing at the time of study entry, an archival FFPE tumor tissue specimen, which may have been collected at any time prior to Screening, can be submitted for analysis. Specimens used to confirm diagnosis or collected after the participant has been diagnosed with metastatic disease will be preferred for determination of PD-L1 status. Both archival tissue block and freshly cut slides are acceptable. If no archival FFPE tumor tissue is available, a fresh tumor tissue biopsy should be obtained and tested.

8. Participant has an ECOG performance status score of 0 or 1.
9. CCI [redacted]
10. Participant has adequate organ function as defined in Table 6. (**Note:** A complete blood count test should be obtained without transfusion or receipt of colony-stimulating factors within 2 weeks of obtaining the sample.)

Table 6: Adequate Baseline Organ Function Inclusion Criteria

CCI [redacted]

11. Participant has recovered to Grade ≤1 from any prior treatment-related toxicities at the time of randomization. A participant with Grade 2 alopecia is an exception to this criterion.
12. Contraceptive use by male and female participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants are eligible to participate if they agree to the following during the Treatment Period and for at CCI [redacted] after the last dose of study treatment (Note: Duration of contraceptive use after the last dose of docetaxel must be consistent with local requirements and the local approved product label; however, the minimum duration is CCI [redacted] after the last dose of docetaxel):

- Refrain from donating sperm

plus, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

or

- Must agree to use contraception/barrier as follows:

– Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.
– Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

Note: If instructed in the local label, the Investigator should advise fertile male participants receiving docetaxel to consider collecting and storing viable sperm prior to undergoing treatment given that docetaxel has genotoxic effects and may alter male fertility.

b) A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:

- Is a woman of nonchildbearing potential (WONCBP), as defined in APPENDIX 6.

OR

- Is a WOCBP, as defined in APPENDIX 6, using a contraceptive method that is highly effective (with a failure rate of <1% per year and, preferably, with low user dependency, as described in APPENDIX 6) during the Treatment Period and for at least [redacted] after the last dose of study treatment and agrees not to donate eggs (ova or oocytes) for the purpose of reproduction during this period. (Note: Duration of contraceptive use after the last dose of docetaxel must be consistent with local requirements and the local approved product label; however, the minimum duration is [redacted] after the last dose of docetaxel). The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance or recently initiated) in relationship to the first dose of study treatment.

– A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local guidelines) within 72 hours before the first dose of study treatment. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Note the following:

– Additional requirements for pregnancy testing during and after study treatment are located in Section 8.4.6.
– The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant has been previously treated with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent that resulted in permanent discontinuation due to an AE.
2. Participant has been previously treated with an anti-TIM-3 or anti-CTLA-4 agent or docetaxel.
3. Participant has a documented sensitizing EGFR, ALK, or ROS-1 mutation. Participants whose tumors have not been tested for these driver mutations and therefore who have unknown driver mutation status are not eligible. Participants with squamous histology do not need to be tested for these driver mutations.
4. Participant had radiological or clinical disease progression (ie, worsening performance status, clinical symptoms, and laboratory data) ≤8 weeks after initiation of prior anti-PD-1 or anti-PD-L1 antibody. The clinical disease progression should have been confirmed by a subsequent radiological scan.
5. Participant has received radiation to the lung that is >30 Gy within 6 months prior to the first dose of study treatment.
6. Participant has completed palliative radiotherapy within 7 days prior to the first dose of study treatment.
7. Participant is ineligible if any of the following hepatic characteristics are present:

a) Alanine aminotransferase (ALT) >2.5×ULN
b) ALT and/or aspartate aminotransferase (AST) >1.5×upper limit of normal (ULN) concomitant with alkaline phosphatase (ALP) >2.5×ULN
c) Bilirubin >1×ULN
d) Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones, liver metastases, or otherwise stable chronic liver disease per the Investigator's assessment)

Note: Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis.

CCI



CCI [redacted]

11. Participant has known new or progressive brain metastases and/or leptomeningeal metastases. Participants who have received prior therapy for their brain metastases and have radiologically stable central nervous system disease may participate, provided they are neurologically stable for at least 4 weeks before study entry and are off corticosteroids within 3 days prior to the first dose of study treatment.
12. Participant has tested positive for the following at Screening or within 3 months before the first dose of study treatment:
    a. Presence of hepatitis B surface antigen.
    b. Presence of hepatitis C antibody in the absence of an RNA test for hepatitis C virus. If a confirmatory RNA test is available, a positive test result will exclude a participant, while a negative test result (indicating absence of active infection) will allow the participant to enter into the study.
13. CCI [redacted]
14. Participant has known HIV (positive for HIV-1 or HIV-2 antibodies).
15. Participant has active autoimmune disease that required systemic treatment in the past 2 years, is immunocompromised in the opinion of the Investigator, or is receiving systemic immunosuppressive treatment. (**Note:** Participants with splenectomy are allowed.) Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy up to 5 mg of prednisone, or equivalent, for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. **Note:** Participants who have received or are receiving low dose prednisone (up to 5 mg daily) or dexamethasone (up to 0.8 mg daily), or equivalent, as needed to manage certain chronic medical conditions, are eligible. During treatment, a high dose steroid can be used to manage an acute condition only for a short time (see Table 8).
16. CCI [redacted]
17. Participant has symptomatic ascites or pleural effusion. A participant who is clinically stable following treatment of these conditions (including therapeutic thoracentesis or paracentesis) is eligible.

18. Participant has current interstitial lung disease, current pneumonitis, or a history of pneumonitis that required the use of oral or IV glucocorticoids to assist with management. Lymphangitic spread of the NSCLC is not exclusionary.

CCI [redacted]

21. Participant has pre-existing peripheral neuropathy that is Grade ≥2 by National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 criteria.
22. Participant has received a live vaccine within 30 days of the first dose of study treatment. Seasonal flu vaccines that do not contain live virus and Coronavirus Disease 2019 (COVID-19) vaccines (see Section 6.9) are permitted.

CCI [redacted]

25. Participant is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) for undergoing a biopsy procedure (in cases when a participant does not have an archival biopsy), other than an aspirin dose ≤1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

CCI [redacted]

Note: See APPENDIX 11 for additional exclusion criteria for participants in the United Kingdom.

5.3. Lifestyle Considerations

Participants must adhere to the contraception guidelines in Section 5.1.

5.3.1. Dietary Restrictions

As docetaxel is metabolized by CYP3A4, participants should abstain from ingestion of any food or drink containing grapefruit or grapefruit juice, Seville oranges, or pomelos within 3 days prior to the first dose of study treatment(s) and until 3 days after their last dose of study treatment.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomized into the study. Laboratory results obtained during Screening should be used to determine eligibility criteria. In situations where laboratory results are outside the permitted range, the Investigator may opt to retest the participant and the subsequent screening result, if within range, may be used to confirm eligibility. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

CCI [redacted] CCI [redacted] publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations, and any serious adverse events (SAEs).

5.5. Criteria for Temporarily Delaying Administration of Study Treatment

Planned dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (eg, elective surgery, unrelated medical events, participant vacation, or holidays). **Note:** For participants in Arms A and B receiving triple or double combination therapy, all components of study treatment must be delayed in the event of a planned dosing interruption as the study treatments must be administered together. Participants should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise agreed with the Sponsor. The reason for interruption or discontinuation of treatment should be recorded in the eCRF.

6. STUDY TREATMENTS AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Treatments Administered

Study treatments to be administered in this study are summarized in Table 7 and Section 6.1.1, Section 6.1.2, and Section 6.1.3. For further details, refer to the Pharmacy Manual (cobolimab and dostarlimab) or to the product label (docetaxel).

Table 7: Study Treatments for Study 213410

Arm Name	**Cobolimab**	**Dostarlimab**	**Chemotherapy Standard of Care** **(all arms)**
Treatment name	Cobolimab	Dostarlimab	Docetaxel
Type	Biologic	Biologic	Drug
Dose formulation	Solution	Solution	Solution
Unit dose strength	300 mg Q3W	500 mg Q3W	75 mg/m^2 Q3W
Route of administration	IV infusion	IV infusion	IV infusion
Use	Experimental	Experimental	Background treatment
IMP	IMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	May be provided centrally by the Sponsor or locally by the study site
Packaging and labeling	Study treatment will be provided in a single-use vial. Each vial will be labeled as required per country requirements.	Study treatment will be provided in a single-use vial. Each vial will be labeled as required per country requirements.	Study treatment will be centrally or locally obtained.[1]

Abbreviations: ICF=informed consent form; IMP=investigational medicinal product; IV=intravenous; Q3W=every 3 weeks; SRM=Study Reference Manual.
Note: These formulation details are current at the time of protocol finalization and may be updated in other documents (eg, SRM and/or ICF) without requiring protocol amendment.
[1] Obtained as commercially available formulation for IV infusion.

6.1.1. Cobolimab

Cobolimab for IV infusion will be supplied by the Sponsor as a solution of l[redacted]

Cobolimab will be administered through a 30 (-5 and +15)-minute IV infusion at a dose of 300 mg Q3W. Cobolimab may be administered until disease progression, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.

Sites should make every effort to target the infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, however, a window between -5 and +15 minutes is permitted.

If a participant is receiving cobolimab as study treatment (Arm A), cobolimab will be administered first (followed by dostarlimab second and docetaxel third).

6.1.2. Dostarlimab

Dostarlimab for IV infusion will be supplied by the Sponsor as a solution of [redacted]

Dostarlimab will be administered through a 30 (-5 and +15) minute IV infusion at a dose of 500 mg Q3W. Dostarlimab may be administered until confirmed disease progression, unacceptable toxicity, participant withdrawal, Investigator's decision, or death.

Sites should make every effort to target the infusion timing to be as close to 30 minutes as possible. Given the variability of infusion pumps from site to site, however, a window between -5 and +15 minutes is permitted.

If a participant is receiving dostarlimab in combination with cobolimab (Arm A), dostarlimab will be administered second (ie, after cobolimab). If a participant is receiving dostarlimab and docetaxel only (Arm B), dostarlimab will be administered first, before docetaxel.

6.1.3. Docetaxel

Docetaxel is a commercially available chemotherapeutic agent and will be administered at 75 mg/m^2 via a 60-minute IV infusion Q3W for a minimum of 4 cycles. Docetaxel infusion time is based on the product label; institutional discretion on this parameter is not allowed. A variance between the actual dose and the calculated dose (based on the participant's BSA) is permitted per local practice e.g. where BSA is not recalculated to accommodate weight fluctuations or where dose banding or capping are used. Docetaxel should be administered until disease progression or unacceptable toxicity (see Section 7.1) or according to local practice and the local approved product label. Docetaxel for injection may be supplied by the Sponsor or may be obtained locally as a commercially available dosage formulation with reimbursement by the Sponsor.

The docetaxel package insert contains descriptions of the packaging of docetaxel and instructions for preparation and administration. All participants should be premedicated with oral or injectable steroids according to the approved product label and/or standard practice. Additional premedication should be administered as per standard practice.

6.2. Preparation/Handling/Storage/Accountability

Preparation

The Pharmacy Manual contains specific instructions for the preparation of study treatment and administration of the infusion solution. During the Treatment Period, all study treatments will be prepared by an unblinded pharmacist or designee and dispensed in an unblinded manner to the study staff for administration to participants.

Handling and Storage (Including Disposal)

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received. Any discrepancies must be reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.
3. Precaution will be taken to avoid direct contact with the study treatment. A Safety Data Sheet describing occupational hazards and recommended handling precautions will be provided to the Investigator. In the case of unintentional occupational exposure, the Site Monitor, GSK Medical Monitor, and/or GSK study contact should be notified.
4. At the end of the study, when all participants have discontinued study treatment, complete drug reconciliation per batch should be available at the site for verification in order to allow drug destruction or return procedure. After receiving Sponsor approval in writing, the investigational site is responsible for destruction of the study treatment according to local regulations. If a site does not have the capability for onsite destruction, the Sponsor will provide a return for destruction service through a third party. Both the unused and expired study treatment must be destroyed, upon authorization of the Sponsor, according to local regulations and procedures, and a copy of the destruction form must be filed in the study binder.
5. The medication provided for this study is to be used only as indicated in this protocol and only for the participants entered in this study.
6. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

Accountability

1. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, dispensation, reconciliation, and final disposition records) throughout the study.
2. Details of maintaining drug accountability, including information on the accountability log, will be provided in the Pharmacy Manual.

3. All dispensation and accountability records will be available for Sponsor review. The Study Monitor will assume the responsibility for reconciling the study treatment accountability log. The pharmacist will dispense study treatment for each participant according to the protocol and Pharmacy Manual, if applicable.

6.3. Measures to Minimize Bias

6.3.1. Method of Treatment Assignment – Randomization

Following informed consent and completion of all Screening assessments, participants who meet the inclusion and exclusion criteria will be randomized in a 2:2:1 ratio to Arms A, B, or C, receiving cobolimab + dostarlimab + docetaxel, dostarlimab + docetaxel, or docetaxel alone, respectively, as study treatment. Randomization will be completed in an unblinded manner. Randomization will be stratified by the following 3 factors: Prior lines of therapy (1 prior line vs 2 prior lines), PD-L1 status (TPS≥50% vs TPS <50%), and histology (squamous vs nonsquamous).

It is recommended that participants receive the first dose of study treatment on the day of randomization. If Screening assessments were performed within 72 hours of Day 1, repeat testing is not required.

6.3.2. Method of IA

See Section 9.3.2 and APPENDIX 5.

6.4. Planned Dose Adjustments

6.4.1. Dose Levels and Dose Adjustment

6.4.1.1. Cobolimab and Dostarlimab

Cobolimab and/or dostarlimab dose reductions (Arms A and B only) are **not permitted**.

6.4.1.2. Docetaxel

Docetaxel dose reduction

Per study protocol, Docetaxel must only be dose reduced to 55 mg/m^2.

Participants can have a maximum of 1 dose modification of docetaxel to 55 mg/m^2 throughout the course of the study for toxicities. Participants who require a second dose modification should be discontinued from docetaxel treatment.

Refer to the local docetaxel label for all docetaxel dose modification guidelines as to when to dose reduce. This section below serves as a guide to investigators for when to dose reduce docetaxel and does not replace Investigator judgment and applicable local label recommendations, if more stringent.

As per the label, docetaxel treatment in NSCLC may be modified as follows: for febrile neutropenia, neutrophils <500 cells/mm^3 for >1 week, severe or cumulative cutaneous reactions, or other Grade 3/4 nonhematological toxicities, withhold until resolution of the toxicity and then resume at a reduced dose of 55 mg/m^2 (Docetaxel Prescribing Information, 2019).

Participants who develop Grade ≥3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

In the event of elevated bilirubin docetaxel should be discontinued.

In the event of any other elevations in transaminases management guidelines should follow the local docetaxel label.

If a docetaxel dose reduction for toxicity occurs, then the dose may not be re-escalated.

If a participant experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity).

Docetaxel Dose Delay

- **If the participant is experiencing an AE, docetaxel dose can be delayed /withheld. In Arms A and B, immuno-oncology (IO) treatment should also be delayed /withheld if docetaxel is being delayed, since all the drugs must be administered together.**
- **Docetaxel can be delayed for a maximum of 6 weeks. Please contact medical monitor if a dose delay occurs. Note**: Participants in Arms A and B (IO + docetaxel combination arms) may discontinue docetaxel and remain on IO treatment (cobolimab and dostarlimab in Arm A and dostarlimab in Arm B)

6.4.2. Guidelines for Events of Special Interest

The severity of AEs will be graded using the NCI-CTCAE v5.0. Guidelines for dose modifications and interruptions for management of common toxicities associated with the study treatment(s) are provided in this section.

6.4.2.1. Management of IO-Related AEs

IO (cobolimab and/or dostarlimab) treatment (Arms A and B only) may be delayed or discontinued due to toxicity. AEs (both nonserious and serious) associated with cobolimab and dostarlimab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of study treatment.

IO treatment must be withheld for study drug-related toxicities, Grade ≥3 toxicities, and certain imAEs, as described in Table 8. The recent joint American Society of Clinical Oncology and National Comprehensive Cancer Network guidelines for the diagnosis and management of imAEs treated with immune checkpoint inhibitor therapy may be used as a supplement to Table 8 (Brahmer, 2018). The maximum allowed drug delay period for the IO treatments is 12 weeks. If IO treatment is delayed, docetaxel should also be delayed. If IO treatment is discontinued for imAEs, docetaxel should also be discontinued.

Table 8: Dose Modifications for imAEs

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
General Instructions Corticosteroid taper should be initiated upon AE improving to Grade ≤1, and taper should continue over at least 4 weeks. For situations where cobolimab and/or dostarlimab have been withheld, treatment (Cobolimab and dostarlimab in Arm A and dostarlimab in Arm B) can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered, unless permanent discontinuation is advised. Cobolimab and/or dostarlimab should be permanently discontinued along with docetaxel if AE does not resolve within 12 weeks of last dose or if corticosteroids cannot be reduced to ≤10 mg prednisone, or equivalent, per day, within 12 weeks. For severe and life-threatening imAEs, IV corticosteroid should be initiated first, followed by oral steroid. Other immunosuppressive treatment should be initiated if imAEs cannot be controlled by corticosteroids.				
Adrenal insufficiency	Grade 2 or 3	Hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrent or worsening Grade ≥2 adrenal insufficiency while adequate HRT is continuing, permanently discontinue study treatment.	Start treatment with corticosteroids before other HRT to avoid adrenal crisis (hydrocortisone slowly titrating doses down according to symptoms or prednisone and fludrocortisone titrating up or down based on BP, other symptoms, and laboratory results); participants with severe symptoms may require additional fluids (eg, saline >2 L).	Monitor for cortisol level (AM), comprehensive metabolic panel (Na, K, CO_2, and glucose), and renin. Ensure adequate evaluation (eg, endocrine consultation).
	Grade 4	Permanently discontinue		

Table 8: Dose Modifications for imAEs (Continued)

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST/ALT elevation or increased bilirubin or hepatitis **See Section 6.4.1.2 for dose management of docetaxel for elevated bilirubin or any transaminase elevations. See Section 7.1.1 for liver chemistry stopping criteria.**	Grade 2 with AST/ALT >3 to 5×ULN or total bilirubin >1.5 to 3×ULN	Restart dosing when toxicity resolves to Grade 0 to 1	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg methylprednisolone or equivalent), followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value[s] return to baseline or are stable). See Section 7.1.1 and APPENDIX 7 for additional details on liver event follow-up assessments.
	Grade ≥3 with AST/ALT >5×ULN or total bilirubin >3×ULN	Permanently discontinue[1]	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent), followed by taper	

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/colitis	Grade 2 or 3	Restart dosing when toxicity resolves to Grade 0 to 1	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent), followed by taper	Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, and blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). Participants with Grade ≥2 diarrhea where colitis is suspected should consider GI consultation and an endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4 or recurrent Grade 3	Permanently discontinue		
Hemophagocytic lymphohistiocytosis	Any grade	Permanently discontinue		

Table 8: Dose Modifications for imAEs (Continued)

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hyperthyroidism	Grade 3	Hold until return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0 to 1.	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 4	Permanently discontinue		
Hypophysitis	Grade 2 or 3	For Grade 2 to 3, hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0 to 1. For recurrence or worsening of Grade ≥2 hypophysitis after steroid taper has been completed and patient is on adequate HRT, permanently discontinue.	Administer corticosteroids and initiate HRT as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 4	Permanently discontinue		

Table 8: Dose Modifications for imAEs (Continued)

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 3	Hold until administration of HRT results in return to adequate hormone levels based on laboratory values and restart dosing when toxicity resolves to Grade 0 to 1	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders. Monitor thyroid function tests. Ensure adequate evaluation (eg, endocrine consultation). Exclude concomitant adrenal insufficiency (AM cortisol level).
	Grade 4	Permanently discontinue		
Immune-mediated encephalitis	Any grade	Permanently discontinue	Consider IV acyclovir until PCR results obtained. Trial with methylprednisolone; if severe, treatment with methylprednisolone. If positive for autoimmune encephalopathy antibody or no improvement after 7 to 14 days, consider rituximab.	Ensure adequate evaluation to confirm etiology and exclude other causes
Infusion-related reaction	See Table 9			

Table 8: Dose Modifications for imAEs (Continued)

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Grade 2, 3, or 4	Permanently discontinue	Administer high-dose corticosteroids (1 g/day of IV methylprednisolone) for 3 to 5 days, followed by oral prednisone taper over 4 to 6 weeks based on improvement in cardiac function and biomarkers. If no improvement in 24 hours, consider adding other potent immunosuppressive agents	Ensure adequate evaluation (eg, urgent cardiology consultation) to confirm etiology and exclude other causes
Pneumonitis	Grade 2	Restart dosing when toxicity resolves to Grade 0 to 1. If Grade 2 recurs, permanently discontinue.	Administer corticosteroids (initial dose of 1 to 2 mg/kg methylprednisolone or equivalent), followed by taper	Monitor participants for signs and symptoms of pneumonitis. Evaluate participants with suspected pneumonitis with radiological imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Table 8: Dose Modifications for imAEs (Continued)

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Renal failure or nephritis	Grade 2 with creatinine >1.5 to ≤3×ULN	Restart dosing when toxicity resolves to Grade 0 to 1.	Start treatment with prednisone; if persistent Grade 2 beyond 1 week, prednisone/methylprednisolone	Monitor participants for signs and symptoms, including monitoring of creatinine and urine protein every 3 to 7 days. Ensure adequate evaluation (eg, nephrology consultation) to confirm etiology and exclude other causes.
	Grade ≥3 with creatinine >3×ULN	Permanently discontinue	Start treatment with prednisone; if persistent Grade 2 beyond 1 week, prednisone/methylprednisolone. Consider adding 1 of the following after 1 week of steroids: azathioprine, cyclosporine, cyclophosphamide, infliximab, or mycophenolate.	Ensure adequate evaluation (eg, nephrology consultation, renal biopsy) to confirm etiology and exclude other causes. Consider inpatient care.
Severe exfoliative dermatologic events	Suspected SJS, TEN, or DRESS	Withhold if suspected	Treat with high potency topical steroids to affected areas. Treat with prednisone.	Ensure adequate evaluation (eg, urgent dermatology consultation) to confirm etiology and exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Administer 1 to 2 mg/kg/day IV methylprednisolone and taper steroid when dermatitis is controlled	
Severe neurological events (myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome[2], transverse myelitis)	Grade 1	Withhold dose. Restart dosing when toxicity resolves to Grade 0.	Consider high dose corticosteroids and other therapies as needed. It is highly recommended that Investigators discuss any AEs with the Sponsor before using infliximab.	Ensure adequate evaluation (eg, neurology consultation). Consider MRI of brain and/or spine depending on symptoms. Consider inpatient management as clinically indicated.
	Grade 2, 3, or 4	Permanently discontinue		

Table 8: Dose Modifications for imAEs (Continued)

imAEs	Toxicity Grade or Conditions (NCI-CTCAE v5.0)	Action Taken with Cobolimab ± Dostarlimab	imAE Management with Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Type 1 diabetes mellitus (T1DM) or hyperglycemia	Grade 3 to 4 hyperglycemia or T1DM (associated with metabolic acidosis or ketonuria)	Restart dosing in appropriately managed clinically and metabolically stable participants; insulin replacement therapy is required	Initiate insulin replacement therapy for participants with T1DM. Administer antihyperglycemic in participants with hyperglycemia.	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Uveitis	Grade ≥2	Withhold	Urgent ophthalmology consultation. Administer treatment with ophthalmic and systemic prednisone/methylprednisolone.	Ensure adequate evaluation (eg, urgent ophthalmology consultation)
	≥Grade 3	Permanently discontinue		
Other imAEs	Based on severity and type of reaction (Grade 2 or 3)	Withhold. Restart dosing when toxicity resolves to Grade 0 to 1	Based on severity of AE, administer corticosteroids. When controlled, taper steroid.	Ensure adequate evaluation to confirm etiology and exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		
Recurrence of imAEs after resolution to Grade ≤1	Grade 1 or 2	Withhold	Based on severity of AEs, administer appropriate treatment until symptoms improve to Grade ≤2.	
	Grade 3 or 4	Permanently discontinue		

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BP=blood pressure; DRESS=drug reaction with eosinophilia and systemic symptoms; GI=gastroenterology; HRT=hormone replacement therapy; imAE=immune-mediated adverse event; IV=intravenous; MRI=magnetic resonance imaging; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PCR=polymerase chain reaction; PD-1=programmed cell death protein-1; SJS=Stevens-Johnson Syndrome; T1DM=Type 1 diabetes mellitus; TEN=toxic epidermal necrolysis; ULN=upper limit of normal.

[1] For participants with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week, then the participants should be discontinued.

[2] In South Korea, permanently discontinue for Grade 1 Guillain-Barré Syndrome.

6.4.2.2. Management of Chemotherapy-Related AEs

Hematological and nonhematological AEs attributable to docetaxel should be managed according to guidelines in the prescribing information and by local institutional practice.

If a toxicity is related to the **combination** of IO therapy (cobolimab or dostarlimab; Arms A and B only) and docetaxel, then the docetaxel dose should be reduced, delayed, or discontinued according to the recommended dose modification, and the IO therapy (cobolimab and dostarlimab in Arm A and dostarlimab in Arm B) should also be delayed or discontinued. Chemotherapy (docetaxel) may be delayed for a maximum of 6 weeks.

6.4.2.3. Management of Infusion-Related Reactions

Participants receiving IV study treatment may develop signs and symptoms of an infusion reaction during or shortly after drug infusion. These reactions generally resolve completely within 24 hours of completion of infusion. Table 9 shows treatment guidelines for participants who experience infusion-related reactions associated with administration of study treatment, including actions to be taken with the study treatment, if necessary.

Table 9 Infusion Reaction Treatment Guidelines

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; treatment not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, or IV fluids); prophylactic medications indicated for ≤24 hours	Stop infusion and monitor symptoms. Additional appropriate medical therapy may include, but is not limited, to the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). The lower infusion rate may be continued for subsequent infusions following discussion with the Medical Monitor. Otherwise, dosing will be withheld until symptoms resolve, and the participant should be premedicated for the next scheduled dose.	Participant may be premedicated 1.5 hours (±30 minutes) prior to infusion with the following: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine) • Acetaminophen 500 to 1,000 mg PO (or equivalent dose of antipyretic)

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment administration.	
Grade 3 Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4** Life-threatening; pressor or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include, but is not limited to, the following: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Participant is permanently discontinued from further study treatment administration.**	No subsequent dosing

Abbreviations: IV=intravenous; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; NSAID=nonsteroidal anti-inflammatory drug; PO=orally.
Note: Appropriate resuscitation equipment should be available in the room, and a physician should be readily available during the period of study treatment administration.

6.5. Participant-Specific Dose Adjustments

There are no participant-specific dose adjustments defined for this protocol.

6.6. Study Treatment Compliance

When participants are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.7. Treatment of Overdose

6.7.1. Protocol-Defined Overdose

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An overdose of docetaxel is defined according to the prescribing information.

In the event of an overdose, the Investigator should do the following:

1. Contact the GSK Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until study treatment of interest can no longer be detected systemically (at least 130 days).
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

See Section 8.5.4 for details on reporting a study treatment overdose.

6.8. Continued Access to Study Intervention after the End of the Study

If a rollover/extension study, expanded access routeinclusive of group program or single patient compassionate use], or [if the product is commercially available and accessible at the time of the EoMS DCO, participants continuing to derive clinical benefit from intervention(s)] may transition to continue treatment. This would depend on what access route(s) are available in a given country.

During the PACT phase, alternative continued treatment access route(s) outside of this study may be implemented, as it becomes available.

6.8.1. Continued Access to Study Intervention After Data Cut-off prior to End of Main Study

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6.9. Concomitant Medications and Nondrug Therapies

Participants should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate.

Prophylactic G-CSF is strongly recommended to avoid complications due to chemotherapy-induced neutropenia.

Participants will be instructed to inform the Investigator prior to starting any new medications from the time of first dose of study treatment until the end of the study (final study visit). Any concomitant medication(s), including nonprescription medication(s) and herbal product(s), taken during the study will be recorded in the eCRF. The minimum requirement is that drug name, dose, and the dates of administration be recorded. Additionally, a complete list of all prior anticancer therapies will be recorded in the eCRF.

Participants can be vaccinated against severe acute respiratory (SARS)-coronavirus 2 (CoV-2) infection ("COVID-19") using vaccines authorized via a limited regulatory mechanism (eg, Emergency Use Authorization) or via accelerated or full approval mechanisms. The use of other candidate COVID-19 vaccines that have not received limited, accelerated, or full authorization, and are only in use as part of a clinical study, is not allowed. COVID-19 vaccination should be done as per local authorization and local health care provider administration.

Questions regarding concomitant medications should be directed to the GSK Medical Monitor for clarification.

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

6.9.1. Prohibited Medications and Nondrug Therapies

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- Strong CYP3A4 inhibitors (while receiving docetaxel)

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7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in APPENDIX 5.

7.1. Discontinuation of Study Treatment

Participants will receive study treatment until any of the following occurs:

- Progressive disease (PD) according to RECIST v1.1 **and*** the participant is clinically unstable, defined as follows:
  - Worsening of performance status
  - Clinically relevant increase in disease-related symptoms
  - Requirement for intensified management of disease-related symptoms (eg, analgesics, radiation, palliative care)

*__Note:__ According to RECIST v1.1, PD alone is **not** a reason to discontinue study treatment. Clinically stable participants should remain on treatment until confirmed PD according to modified Response Evaluation Criteria in Solid Tumors v1.1 for immunotherapies (iRECIST)-confirmed progressive disease (iCPD) occurs.

- Death
- Unacceptable toxicity or other AE that cannot be managed by dose modifications (including meeting stopping criteria for liver chemistry defined in Section 7.1.1

Note: Per the end of study definition (see Section Liver Chemistry Stopping Criteria7.1.1) the study cannot be closed while there are still participants deriving clinical benefit from ongoing study treatment.

In addition, study treatment must be permanently discontinued for any of the following reasons:

- Discontinuation is requested by the participant or proxy (withdrawal of consent by participant or proxy).
- Participant is lost to follow-up.
- It is in the best interest of the participant as judged by the Investigator and/or Sponsor.
- Participant becomes pregnant.

In addition, study treatment **may** be permanently discontinued for any of the following reasons:

- There is a deviation(s) from the protocol.

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

Participants that have discontinued treatment without disease progression should be imaged as per the imaging schedule until disease progression by RECIST v1.1 irrespective of initiation of follow-up anti-cancer therapy. This includes patients that have been randomized but not treated.

All participants who permanently discontinue study treatment without disease progression will be followed for disease progression according to the protocol schedule until death or study closure.

All participants who permanently discontinue study treatment will be followed every 90 days for survival and new anticancer therapy, including radiotherapy. Contact to assess survival can be made via, telephone or email.

Survival follow-up will continue until the study end (see Section 4.4 for definition).

If the participant voluntarily discontinues from treatment due to toxicity, "adverse event (AE)" will be recorded as the primary reason for permanent discontinuation on the eCRF.

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

All participants who discontinue from study treatment will have Safety Follow Up assessments at the time of discontinuation at 30 days (+/- 7days) and 90 days (+/- 7days) after the last dose of study treatment or until the participant starts alternate anticancer therapy as specified in the schedule of activities (SoA) (Table 3). EOT visit may replace the 30-Day Safety Follow Up Visit only if the visits fully coincide using the protocol windows.



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7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons. This is expected to be uncommon. All participants must be followed for survival, up to the EoS as defined in the protocol. Discontinuation of study treatment does not impact a participant's participation in the study. The participant should comply to the protocol schedule of assessments including OS follow up and data collection should continue.

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- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Table 3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If a participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws consent, the Investigator must not access the patient's medical record or other confidential records requiring the consent for purposes of the study unless the patient expressly agreed to continued collection of their medical records for disease history and survival information until the end of the study. Study data related to the patient collected prior to the patient's withdrawal from the study or loss to follow-up is permitted to be retained. CCI

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7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant, reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study.

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8. STUDY ASSESSMENTS AND PROCEDURES

8.1. General Guidelines

- Study procedures and their timing are summarized in the SoA (Table 3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.1. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic

Due to the significant challenges that currently face the healthcare system and participants due to COVID-19, as well as the potential for enduring or additional quarantine measures, the following guidance is being provided in this protocol. In the spirit of global diversity in the COVID-19 pandemic and its impact on healthcare in each individual country, as well as the recently issued guidance by several regulatory authorities, the autonomy of each investigative site to assess the benefit/risk for their participants in clinical studies should be maintained.

Prior to utilization of any of the measures outlined in this section, discussion and approval must be obtained from Sponsor/contract research organization.

It is expected that sites participating in clinical studies will make every effort to ensure proper monitoring and well-being of enrolled participants by adhering to safety monitoring as outlined in the SoA (Table 3). The use of local laboratories and local radiology centers to reduce the need for a participant to come into the clinic is supported, if deemed necessary for the well-being of the participant, including due to the COVID-19 pandemic. These local facilities should be added to regulatory documents, as required.

Additionally, regulatory guidance issued in response to the COVID-19 pandemic supports the use of central and remote monitoring programs to maintain oversight of clinical sites. Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor/contract research organization.

Any restrictions in place at the site that will impact monitoring and/or participant access to the site and care providers should be communicated to the Sponsor/contract research organization.

A global telemedicine platform that allows for continued monitoring of AEs, concomitant medications, protocol deviations, etc, may be engaged. Discussions around utilization of this technology should be held on a per-site basis, and appropriate documentation of utilization should be captured.

In general and if possible, for participants with limited possibility to travel or decreased capacity to come to the clinic, replace nondosing in-person visits with telephone contact or alternative location for assessment (eg, local laboratories and imaging centers, at-home collection of PROs).

Table 11: Critical Data Collection and Safety Precautions

Assessment	Recommendation
PROs (Treatment Period)	May be collected via interview over the telephone or collected electronically via the internet (screen share).
CBC (including additional assessments during the Treatment Period while a participant is receiving docetaxel if required by local guidance)	Local laboratory, if possible. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the Investigator for review.
Serum chemistry	Local laboratory, if possible. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the Investigator for review.
Pregnancy test (including additional monthly testing through 180 days post-treatment)	Local laboratory, if possible. Arrangements for the use of a local laboratory should be made by the site including the reporting of results to the Investigator for review. Per the ICF, the participant must avoid getting pregnant.
Evaluation of response	CT/MRI if possible.

Assessment	Recommendation
PD	CT/MRI if possible.
AEs	Ongoing AEs and SAEs reviewed by telephone. If hematologic AEs are ongoing, a local CBC is desirable. New AEs/SAEs- may be assessed by telephone (SAE documentation should be submitted within 24 hours of learning of the event).
Concomitant medications	Reviewed by telephone and via medical record review.
Other follow-up assessments (EOT and later)	Contact participant by telephone. This discussion should include assessment of new therapies and overall survival.

Abbreviations: ADA=antidrug antibody; AE=adverse event; CBC=complete blood count; CT=computed tomography; EOT=End-of-Treatment; ICF=informed consent form; MRI=magnetic resonance imaging; PD=progressive disease; PK=pharmacokinetic; PRO=patient-reported outcome; SAE=serious adverse event.

8.2. Screening and Critical Baseline Assessments

8.2.1. Baseline Assessments at Screening

Refer to the SoA (Table 3) for the full list of assessments collected during the Screening Period of this study.

8.2.2. Baseline Documentation of Target and Nontarget Lesions

- All baseline lesion assessments must be performed within 28 days prior to the first dose.
- Lymph nodes that have a short axis of <10 mm are considered nonpathological and should not be recorded or followed.
- Pathological lymph nodes with <15-mm and ≥10-mm short axis are considered nonmeasurable.
- Pathological lymph nodes with ≥15-mm short axis are considered measurable and can be selected as target lesions; however, lymph nodes should not be selected as target lesions when other suitable target lesions are available.
- Measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, recorded, and measured at Baseline. These lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

  Note the following:

  – Cystic lesions thought to represent cystic metastases and lesions that have been previously biopsied should not be selected as target lesions when other suitable target lesions are available.

  - Measurable lesions that have been previously irradiated and have not been shown to be progressing following irradiation should not be considered as target lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered measurable. Bone scans, fluorodeoxyglucose-positron emission tomography (FDG-PET) scans, or X-rays are not considered adequate imaging techniques to measure bone lesions.
- All other lesions (or sites of disease) should be identified as nontarget and should also be recorded at Baseline. Nontarget lesions will be grouped by organ. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.
- Prior to study entry, participants must have a baseline tumor assessment of the chest, abdomen, and brain (as well as other regions known to have disease involvement).
  - This assessment should be conducted by CT or MRI scan; CT with contrast is preferred. MRI should be used only if clinically appropriate, when CT is contraindicated, and, preferably, for imaging of the brain. **Note:** MRI of the chest should not be substituted for CT of the chest, even if IV contrast is contraindicated. In such a case, CT will be performed without contrast to evaluate the lung parenchyma. Positron emission tomography (PET)/CT may be used according to RECIST v1.1 guidelines, with full radiation dose diagnostic CT, and as clinically indicated.
  - If a participant has brain metastasis identified at Baseline which are selected as Target or Non-Target lesions those brain lesions should be imaged at every scheduled imaging visit. The modality used for brain imaging should be kept consistent across all imaging visits (i.e. Brain MRI at baseline means that brain MRI should be repeated at each subsequent imaging visit).
  - If a participant had a tumor assessment of the clinically indicated areas within the 28-day screening window before dosing on Cycle 1/Day 1, but prior to signing the main ICF, then an additional CT/MRI scan for study screening is not required. CT/MRI scans completed during Screening prior to signing the main ICF must have been performed and available for submission per the Image Acquisition Guidelines.

8.2.3. Determination of PD-L1 Status Prior to Randomization

To be eligible for the study, participants must have documented PD-L1 status by the CCI [redacted] (please refer to SRM for a list of approved LDTs). If a prior PD-L1 result by 1 of these testing methods is not available at the time of Screening, the participant must submit archival or fresh tumor tissue to be tested locally using 1 of these testing methods, or, if not available, submit for central testing by CCI [redacted]. Results of baseline PD-L1 status assessment are required for stratification and must be available prior to randomization. Participants who do not have documented PD-L1 status by the CCI [redacted] archival or fresh tissue sample will not be eligible for the study.

8.3. Efficacy

8.3.1. Evaluation of Anticancer Activity

- The efficacy of each treatment will be evaluated by assessment of tumor response according to RECIST v.1.1 (APPENDIX 1) by Investigator assessment and/or iRECIST (APPENDIX 2) by Investigator assessment. Both assessment modalities will be used to assess tumor response and disease progression and make treatment decisions. This study includes iRECIST (by Investigator assessment) because it is considered the most up-to-date tumor response criteria for immunotherapy treatments.
- Tumor assessment method and timing, evaluation of disease, disease progression, and response criteria will be conducted according to RECIST v1.1 and iRECIST as follows:
  - Tumor assessment modalities may include imaging (eg, CT or MRI). Assessments should be conducted by CT or MRI scan; CT with contrast is preferred. MRI should be used only if clinically appropriate, when CT is contraindicated, and, preferably, for imaging of the brain. **Note:** MRI of the chest should not be substituted for CT of the chest, even if IV contrast is contraindicated. In such a case, CT will be performed without contrast to evaluate the lung parenchyma. PET/CT may be used according to RECIST v1.1 guidelines, with full radiation dose diagnostic CT, and as clinically indicated.
  - To support continued tumor assessment while on study, serial imaging will be performed Q6W (every 42 [±7] days) for the first 3 scheduled on-study scans and CCI [redacted]
  - At each postbaseline assessment, scans of chest, abdomen, and of the sites of disease identified by the initial scans or any other clinically indicated areas are required. The same imaging technique and anatomical coverage should be used in a participant throughout the study.
  - PD should be confirmed by iRECIST assessments at a minimum of 4 weeks and up to 8 weeks after the first PD assessment. Clinically stable participants should not be discontinued until disease progression is confirmed.
  - For confirmation of response (complete response [CR]/PR), every attempt should be made to stay on the original imaging schedule. If a confirmation of response scan is needed earlier that the next regularly scheduled imaging visit, it should be acquired at least 4 weeks after the first indication of response (CR/PR).
  - For postbaseline assessments, a window of ±7 days is permitted to allow for flexible scheduling. If the last radiological assessment was more than the scheduled number of weeks prior to the participant's withdrawal from study and PD has not been documented, then a disease assessment should be obtained at the time of withdrawal from study.
  - To ensure comparability between the baseline and subsequent assessments, the same method of assessment and the same imaging technique will be used when assessing response.

8.3.1.1. Overall Survival

OS as a primary and secondary efficacy endpoint in this study is defined as survival from the date of randomization to the date of death by any cause. Following the EOT Visit, survival status will be collected for all participants using acceptable means, including telephone contact. Participants without documented death at the time of the final analysis will be censored at the last date they were known to be alive.

8.3.1.2. Objective Response Rate

ORR as a secondary endpoint in this study will be evaluated by RECIST v1.1 based on Investigator assessment and will be defined as the proportion of participants who have achieved cCR or cPR.

ORR as an exploratory endpoint in this study will be evaluated using iRECIST based on Investigator assessment and will be defined as the proportion of participants who have achieved cCR or cPR.

8.3.1.3. Progression-Free Survival

PFS as a secondary efficacy endpoint in this study will be evaluated using RECIST v1.1 based on Investigator assessment and will be defined as the length of time until disease progression, from the time of randomization to the earliest date of assessment of disease progression or death by any cause.

PFS as an exploratory efficacy endpoint in this study will be evaluated using iRECIST based on Investigator assessment and will be defined as the length of time until confirmed disease progression from the time of randomization to the earliest date of iRECIST iCPD or death by any cause.

8.3.1.4. Duration of Response

DOR as a secondary efficacy endpoint in this study will be evaluated using RECIST v1.1 based on Investigator assessment and will be defined as the time from first documented response (CR/PR) until the time of first documentation of disease progression or death, whichever occurs first.

8.4. Safety

Refer to the SoA (Table 3) for full list of safety assessments and their timing during this study.

8.4.1. Physical Examinations

- A full physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Symptom-directed physical examinations will include assessments based on participants' current symptoms and may include brief examination of the lungs, cardiovascular system, and abdomen (liver and spleen).

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.4.2. ECOG Performance Status

- Performance status will be assessed using the ECOG performance status scale (APPENDIX 3). The same observer should assess performance status each time, if possible.

8.4.3. Vital Signs

- Vital signs are to be measured in a semisupine position after a 5-minute rest and will include temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and oxygen saturation (measured by pulse oximetry).
- Vital signs will be measured more frequently if warranted by clinical condition of the participant. On days where vital signs are measured multiple times, temperature does not need to be repeated, unless clinically indicated.
- Height (at Screening only) and weight will also be measured and recorded.

  Note: For height and weight measurements, the participant is allowed to wear indoor, daytime clothing with no shoes.

8.4.4. Electrocardiograms

- All participants will undergo electrocardiograms (ECGs). Participants will be in a supine or semirecumbent position (about 30 degrees of elevation) and rested for approximately 2 minutes before ECGs are recorded.

8.4.5. Clinical Safety Laboratory Assessments

- See APPENDIX 4 for the full list of clinical laboratory tests to be performed and the SoA (Table 3) for the timing and frequency. Clinical laboratory assessments will be performed by the local laboratory at the investigational site.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. If SAE criteria are met (APPENDIX 10), the event should be recorded and reported according to the SAE reporting process (Section 8.5.4).
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study, or within 90 days after the last dose of study treatment, should be repeated until the values return to normal/baseline or are no longer considered significantly abnormal by the Investigator or GSK Medical Monitor.

- If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor should be notified.
- Hematologic testing may occur more frequently than is specified in the SoA if additional testing is medically indicated per the Investigator judgment or if an event occurs that meets the criteria for study treatment dose adjustment (Section 6.4).
- All protocol-required laboratory tests must be conducted in accordance with the Study Reference Manual, Laboratory Manual, and the SoA (Table 3).
- Additional tests may be performed at a laboratory facility other than the study site, but the test results must be reported to the study site, the study site must keep a copy of the test results with the participant's study file, as well as laboratory reference ranges for the facility used, and the results must be entered into the eCRF.
- If laboratory values from nonprotocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE, AE, or dose modification), then the results must be recorded.
- Further details on sample collection and analysis can be found in the Study Reference Manual and the Laboratory Manual. Any suspected case of secondary cancer reported while a participant is receiving treatment or followed for post-treatment assessments must be investigated, including obtaining and documenting a histological diagnosis. Testing completed as part of standard of care is sufficient as long as the methods are deemed acceptable after consultation with the GSK Medical Monitor.

8.4.6. Pregnancy Testing

- Refer to Section 5.1 for pregnancy testing study entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted prior to each dose of study treatment (within 72 hours).
- Monthly pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure to the study treatment and through at least CCI [redacted], minimum, thereafter, or longer as required by local approved product labels (per the required contraception use in this study; see Section 5.1).
- Additional serum or urine pregnancy tests may be performed, as determined necessary, by the Investigator or required by local regulations, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Any pregnancies that occur in female participants and female partners of male participants will be collected after the start of study treatment and until at least CCI [redacted] following the last dose of study treatment, or longer as per local requirements and local approved product labels, and are to be reported as described in Section 8.5.5.

8.5. AEs, SAEs, and Other Safety Reporting

The definitions of AEs, SAEs, and other safety events can be found in APPENDIX 10.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following-up all events.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in APPENDIX 10.

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

- All AEs and SAEs will be collected from the start of study treatment until the time points outlined in Table 12 and the SoA (Table 3). Any SAEs assessed as related to study participation (eg, study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant provides informed consent.

Table 12: Collecting and Reporting AEs, Pregnancy, and Survival

Parameter	Time Point
AEs	Through 30 days following the last dose of study treatment or until the participant starts alternate anticancer therapy, whichever occurs first
SAEs	Through 90 days following the last dose of study treatment or until the participant starts alternate anticancer therapy, whichever occurs first
Pregnancy	Through at least [redacted] following the last dose of study treatment or as per local requirements and local approved product labels (applies to female participants and female partners of male participants); see Section 5.1 for additional details
Study drug-related SAEs	Until study closeout

Abbreviations: AE=adverse event; SAE=serious adverse event.
Note: All AEs will be collected from the start of study treatment.

- Medical occurrences that begin before the start of study treatment, but after obtaining informed consent, will be recorded as medical history/current medical conditions, not as AEs.
- All SAEs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours, as indicated in APPENDIX 10. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

- Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of a participant's study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

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8.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until the event is resolved, stabilized, or otherwise explained or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in APPENDIX 10.

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.
- An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.
- Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

8.5.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until at least CCI [redacted] following the last dose of study treatment (or per the time period for post-treatment contraception requirements in Section 5.1).
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy of the female participant or female partner of a male participant (after obtaining the necessary signed informed consent from the female partner). Although 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 reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The pregnant female participant or pregnant female partner of a male participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the pregnant female participant or pregnant female partner of a male participant and the neonate, and the information will be forwarded to the Sponsor.
- Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.5.4. Although the Investigator is not obligated to actively seek this information in former study participants/female partners of male study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

8.5.6. Cardiovascular and Death Events

For any cardiovascular events detailed in APPENDIX 10 and all deaths, whether or not they are considered SAEs, specific cardiovascular and death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and noncardiovascular death.The Cardiovascular eCRFs are presented as queries in response to reporting of certain cardiovascular Medical Dictionary for Regulatory Activities (MedDRA) terms. The cardiovascular information should be recorded in the specific cardiovascular section of the eCRF within 1 week of receipt of a cardiovascular event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within 1 week of when the death is reported.

For death due to the disease under study, record the death in the Death eCRF form. For death due to reasons other than the disease under study, record the death in the standard Death Details eCRF form.

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

The following disease-related event (DREs) is common in participants with NSCLC and can be serious/life-threatening:

- Disease progression
  - As this event is typically associated with the disease under study and is an efficacy criterion for this study, it will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of an SAE). Disease progression should be reported within the eCRF DRE pages. If AEs/SAEs occur in relation to disease progression that are not consistent with the natural progression of the participant's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements.

Note: However, if either of the following conditions applies, then the event must be recorded and reported as an AE/SAE (instead of a DRE):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

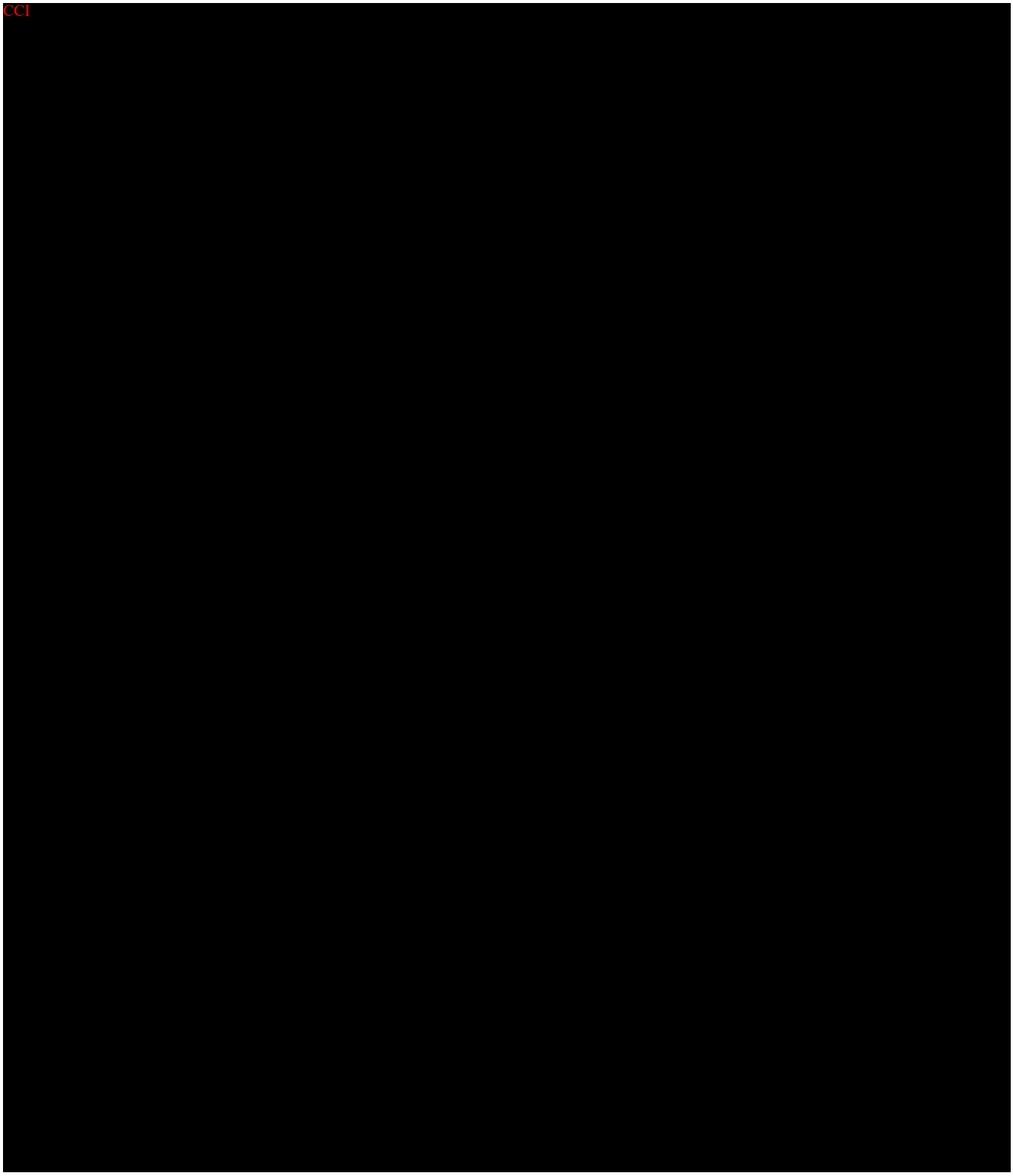
  OR

- The Investigator considers that there is a reasonable possibility that the event was related to study treatment.

8.5.8. Adverse Events of Special Interest

The adverse events of special interest for both dostarlimab and cobolimab are imAEs and infusion-related reactions. These will be programmatically identified by the Sponsor; there is no specific eCRF or action for sites.

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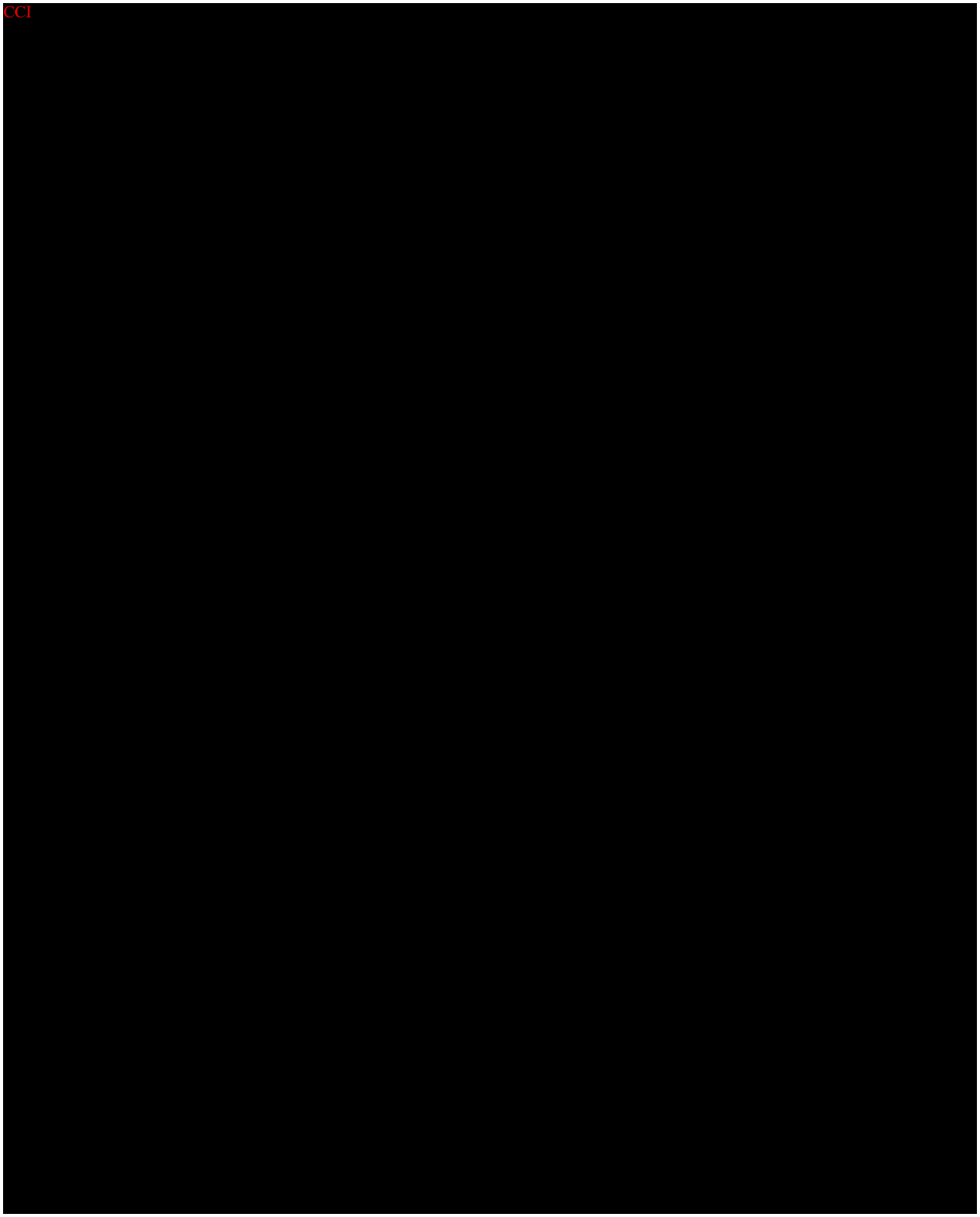
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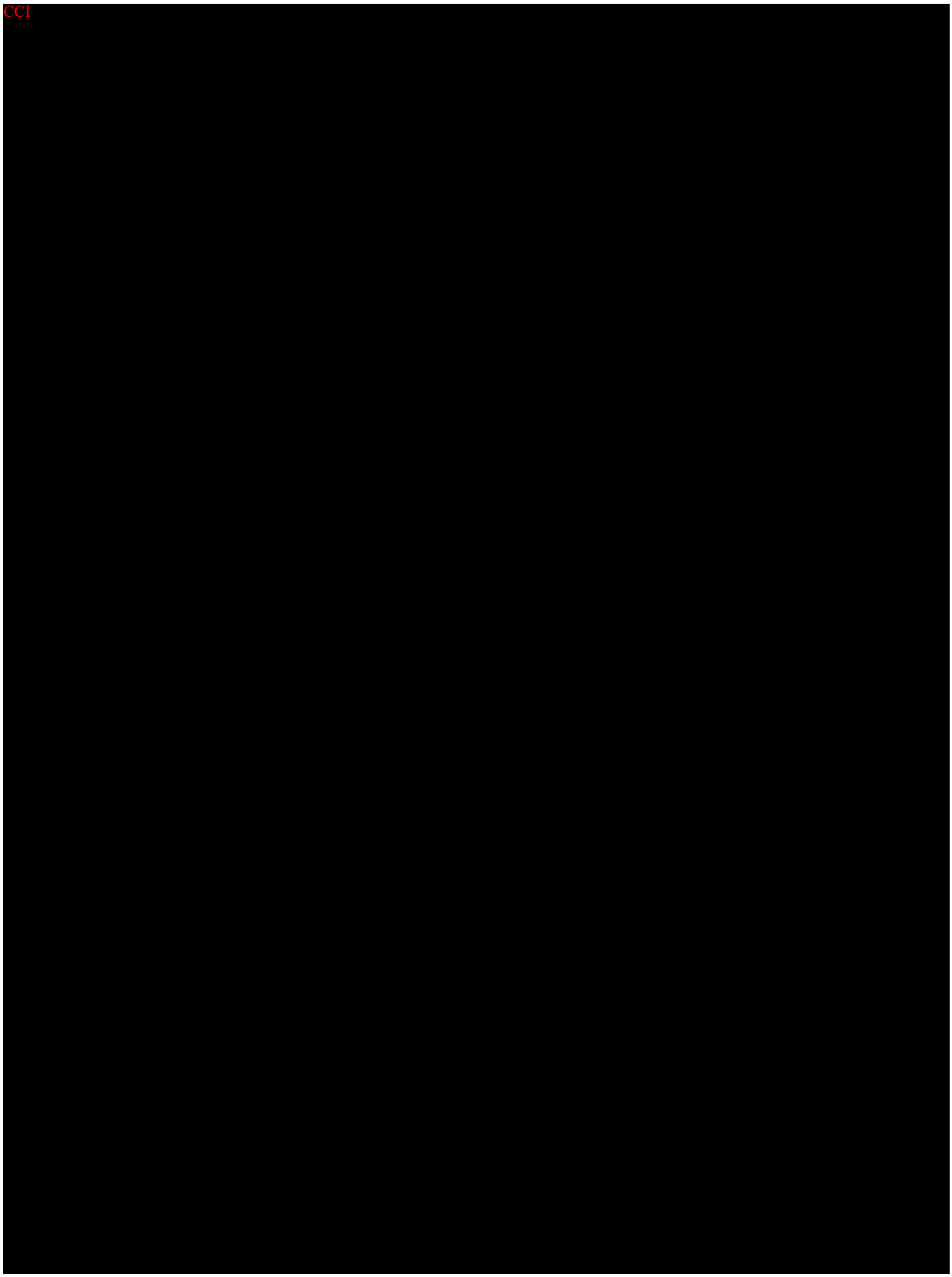
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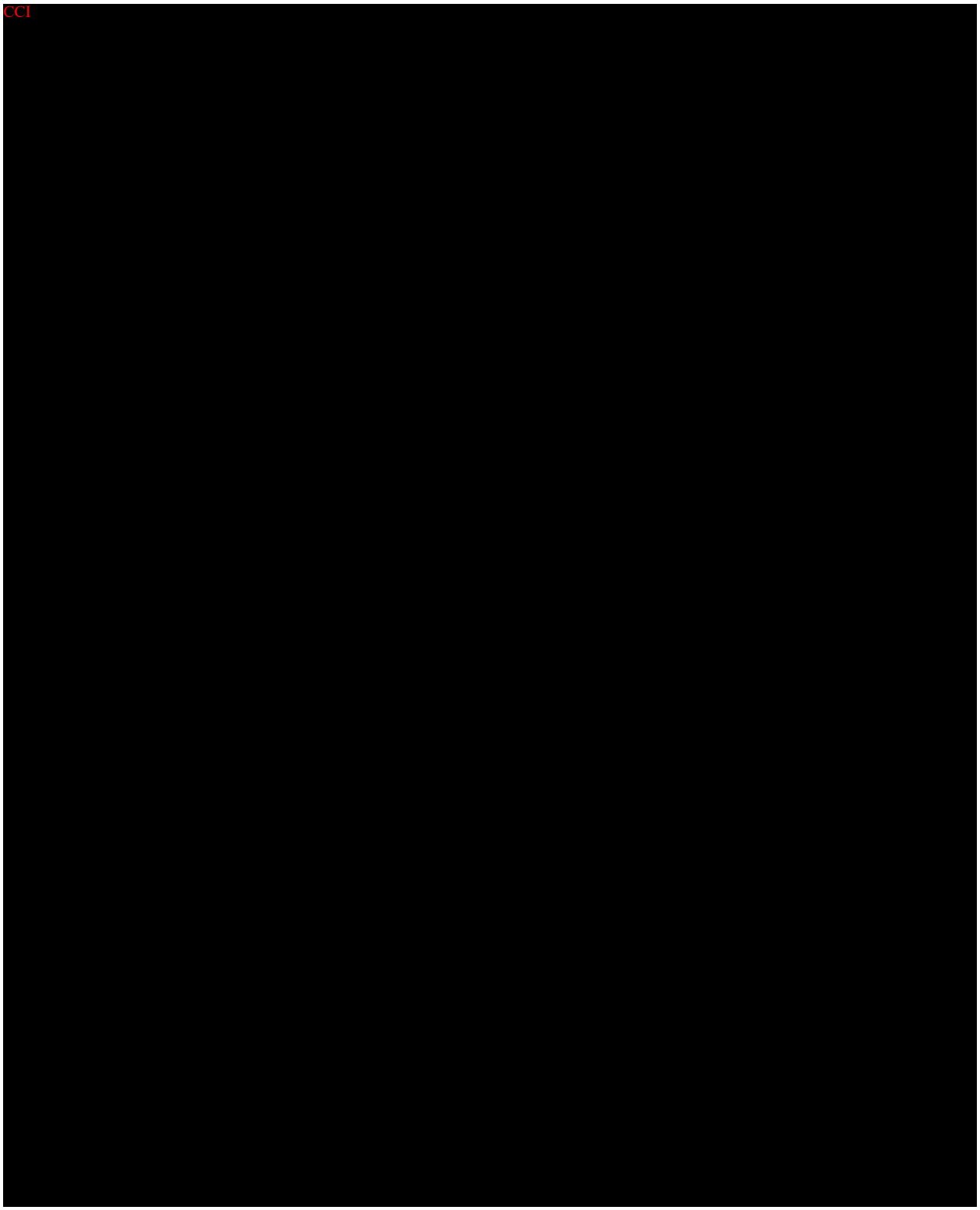
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10. APPENDICES

APPENDIX 1. Guidelines for Assessment of Disease, Disease Progression, and Response Criteria (RECIST v1.1)

Adapted from RECIST v1.1 (Eisenhauer, 2009).

Assessment Guidelines

Please note the following:

- The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate a lesion. Contrast agents must be used in accordance with the Image Acquisition Guidelines.
- All measurements should be taken and recorded in millimeters, using a ruler or calipers.
- Ultrasound is not a suitable modality of disease assessment. If new lesions are identified by ultrasound, then confirmation by computed tomography (CT) or magnetic resonance imaging (MRI) is required.
- Fluorodeoxyglucose-positron emission tomography (FDG-PET) is generally not suitable for ongoing assessments of disease. However, FDG-PET can be useful in confirming new sites of disease where a positive FDG-PET scan correlates with the new site of disease present on CT/MRI. FDG-PET may also be used in lieu of a standard bone scan, providing that coverage allows interrogation of all likely sites of bone disease and FDG-PET is performed at all assessments.
- If PET/CT is performed, then the CT component can only be used for standard response assessments if performed to diagnostic quality, which includes the required anatomical coverage and prescribed use of contrast. The method of assessment should be noted as CT on the electronic case report form.

CT and MRI: Contrast-enhanced CT with 5-mm contiguous slices is recommended.

The minimum size of a measurable baseline lesion should be twice the slice thickness, with a minimum lesion size of 10 mm when the slice thickness is 5 mm. MRI is acceptable, but when used, the technical specification of the scanning sequences should be optimized for the evaluation of the type and site of disease and lesions must be measured in the same anatomic plane by use of the same imaging examinations. Whenever possible, the same scanner should be used (Eisenhauer, 2009).

X-ray: In general, X-ray should not be used for target lesion measurements owing to poor lesion definition. Lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung; however, chest CT is preferred over chest X-ray (Eisenhauer, 2009).

Brain scan: If brain scans are required, then contrast-enhanced MRI is preferable to contrast enhanced CT.

Bone scan (typically bone scintigraphy): If a bone scan is performed and a new lesion(s) is equivocal, then correlative imaging (ie, X-ray, CT, or MRI) is required to demonstrate malignant characteristics of the lesion(s).

Note: PET [FDG or fluoride] may be used in lieu of a standard bone scan, providing coverage allows interrogation of all likely sites of bone disease and PET is performed at all assessments.

Guidelines for Evaluation of Disease

Measurable and Nonmeasurable Definitions

- **Measurable lesion:** A non-nodal lesion that can be accurately measured in at least 1 dimension (longest dimension) of the following:
  - ≥10 mm in long-axis diameter with MRI or CT when the scan slice thickness is no greater than 5 mm. If the slice thickness is greater than 5 mm, the minimum size of a measurable lesion must be at least double the slice thickness (eg, if the slice thickness is 10 mm, a measurable lesion must be ≥20 mm).
  - ≥10-mm caliper/ruler measurement by clinical examination or medical photography.

Additionally, lymph nodes can be considered pathologically enlarged and measurable if the following applies:

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

- **Nonmeasurable lesion:** All other lesions including lesions too small to be considered measurable (longest diameter <10 mm or pathological lymph nodes with ≥10-mm and <15-mm short axis) and truly nonmeasurable lesions, which include leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of the skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques (Eisenhauer, 2009).
- **Measurable disease**: The presence of at least 1 measurable lesion. Palpable lesions that are not measurable by radiological or photographic evaluations may not be utilized as the only measurable lesion.
- **Nonmeasurable only disease**: The presence of only nonmeasurable lesions.

  Note: Nonmeasurable only disease is not allowed per protocol.

Response Criteria

Evaluation of Target Lesions

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

- **Complete response (CR):** Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- **Partial response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters (eg, percent change from baseline).
- **Stable disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.
- **Progressive disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum of diameters recorded since the treatment started (eg, percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- **Not applicable (NA):** No target lesions at baseline.
- **Not evaluable (NE):** Cannot be classified by 1 of the 5 preceding definitions.

Note the following:

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

Evaluation of Nontarget Lesions

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

- **CR:** The disappearance of all nontarget lesions. All lymph nodes identified as a site of disease at baseline must be nonpathological (eg, <10-mm short axis).
- **Non-CR/non-PD:** The persistence of 1 or more nontarget lesion(s) or lymph nodes identified as a site of disease at Baseline with ≥10-mm short axis.
- **PD:** Unequivocal progression of existing nontarget lesions. A modest increase in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- **NA:** No nontarget lesions at baseline.
- **NE:** Cannot be classified by 1 of the 4 preceding definitions.

Note the following:

- In the presence of measurable disease, progression on the basis of solely nontarget disease requires substantial worsening such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
- Sites of nontarget lesions that are not assessed at a particular time point based on the assessment schedule should be excluded from the response determination (eg, nontarget response does not have to be “Not Evaluable”).

New Lesions

- New malignancies denoting disease progression must be unequivocal. Lesions identified in Follow-up in an anatomical location not scanned at Baseline are considered new lesions.
- Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the Investigator until the next scheduled assessment. If, at the next assessment, the new lesion is considered to be unequivocal, progression should be documented.

Evaluation of Overall Response

Table 13 presents the overall response at an individual time point for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions for participants with measurable disease at baseline.

Table 13: Evaluation of Overall Response for Participants with Measurable Disease at Baseline

Target Lesions	Nontarget Lesions	Unequivocal New Lesions	Overall Response
CR	CR or NA	No	CR
CR	Non-CR/non-PD or NE	No	PR
PR	CR, Non-CR/Non-PD, NA or NE	No	PR
SD	CR, Non-CR/Non-PD, NA or NE	No	SD
NE	CR, Non-CR/Non-PD, NA or NE	No	NE
PD	CR, Non-CR/Non-PD, PD, NA or NE	Yes or No	PD
CR, PR, SD, PD, or NE	PD	Yes or No	PD
CR, PR, SD, PD, or NE	CR, Non-CR/Non-PD, PD, NA or NE	Yes	PD

Abbreviations: CR=complete response; NA=not applicable; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

Note the following:

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

Evaluation of BOR

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

- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after randomization at a minimum interval of 84 (±14) days.

- If the minimum time for SD is not met, best response will depend on the subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively, participants lost to follow-up after an SD assessment not meeting the minimum time criteria will be considered not evaluable.

Confirmation Criteria

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

APPENDIX 2. Guidelines for Assessment of Disease, Disease Progression, and Response Criteria for Immunotherapies (iRECIST)

Modified Response Evaluation Criteria in Solid Tumors v1.1 for immunotherapies (iRECIST) is based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and adapted to account for the unique tumor kinetics observed in patients receiving immunotherapeutic drugs. Full iRECIST assessment criteria are detailed in the iRECIST publication (Seymour, 2017) and select details are provided in this appendix. In this study iRECIST will be used to assess tumor response and disease progression and to make treatment decisions. Clinically stable participants should not be discontinued from study treatment until disease progression (as assessed by RECIST v1.1) is confirmed by iRECIST per the assessment rules that follow. The allowance for a participant to continue study treatment despite initial radiological progressive disease (PD) by RECIST v1.1 considers the observation that some participants receiving immunotherapy can experience pseudoprogression, that is, disease response that occurs after an initial assessment of disease progression.

General Assessment Guidelines

It is strongly preferred to obtain repeat tumor imaging for confirmation of PD by iRECIST whenever feasible. Tumor assessment should be repeated at least 4 weeks and up to 8 weeks later to confirm PD by iRECIST.

Images should continue to be sent to the central imaging vendor according to the Imaging Acquisition Guidelines and all data related to iRECIST assessments should be captured in the clinical database.

Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Baseline and Prior to RECIST v1.1 Disease Progression

There is no distinct iRECIST assessment until radiological disease progression based on RECIST v1.1 has occurred.

Assessment and Decision at RECIST v1.1 Disease Progression

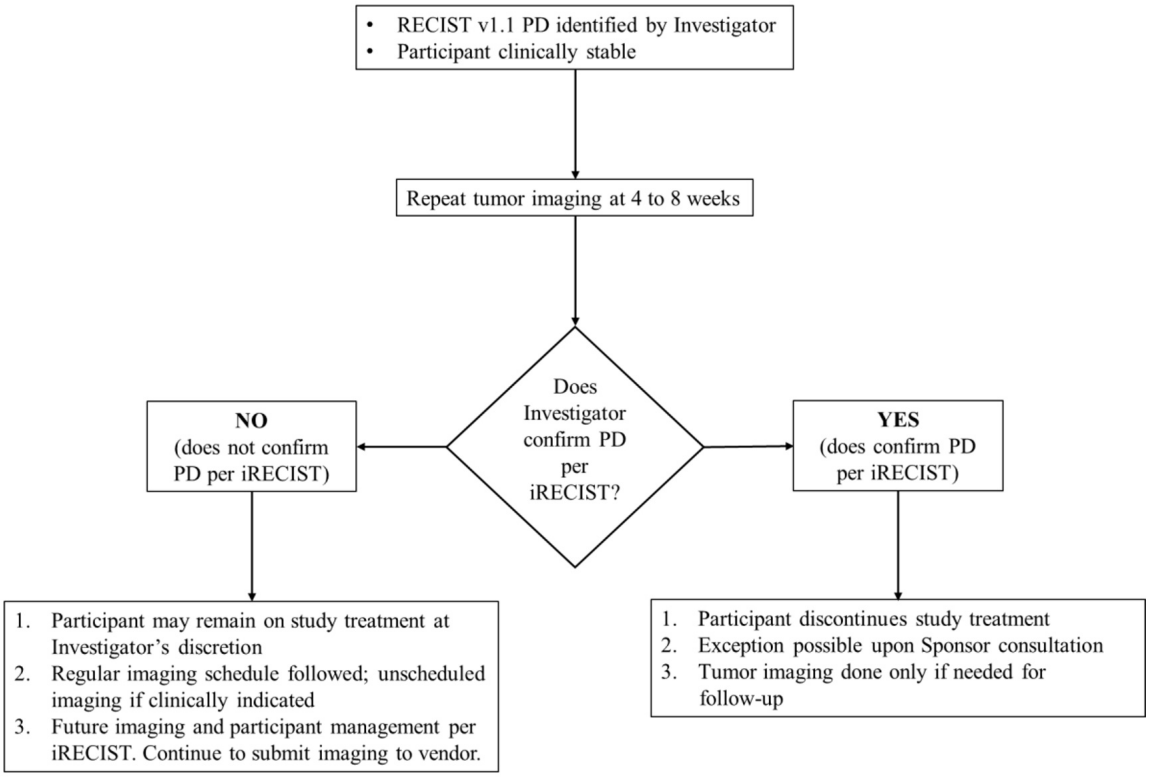
For participants who show evidence of radiological PD by RECIST v1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management; see Table 14 and Figure 3). This decision should be based on the participant's overall clinical condition.

Table 14: Imaging and Treatment after First Radiological Evidence of PD

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiological evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by iRECIST (ie, iCPD) per Investigator assessment	No additional imaging required	Discontinue treatment (exception is possible upon consultation with the Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows iUPD per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. Scan may occur at next regularly scheduled imaging.	Continue study treatment at the Investigator's discretion	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR per Investigator assessment	Continue regularly scheduled imaging and assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging and assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next scan should occur according to the regular imaging schedule.

Abbreviations: iCPD=iRECIST-confirmed progressive disease; iCR=iRECIST-complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors; iSD=iRECIST-stable disease; iUPD=iRECIST-unconfirmed progressive disease; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors.

Figure 3: Imaging and Treatment for Clinically Stable Participants after First Radiological Evidence of PD Assessed by the Investigator



Abbreviations: iRECIST=modified Response Evaluation Criteria in Solid Tumors PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors.

Pseudoprogression may manifest as any factor causing radiological disease progression per RECIST v1.1, including the following, which subsequently resolves:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: The iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST v1.1 terminology.

- Unequivocal progression of non-target lesion(s) identified at Baseline
- Development of new lesion(s)

iRECIST defines response categories including iRECIST unconfirmed progressive disease (iUPD) and iCPD. For the purpose of iRECIST assessment the first visit showing disease progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the disease progression.

At this visit, target and nontarget lesions identified at Baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as were used for Baseline lesion assessment by RECIST v1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as, "New Lesions - Target". The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at Baseline. All other new lesions will be followed qualitatively as, "New Lesions -Nontarget".

Assessment at Confirmatory Imaging

At the confirmatory imaging visit assessment, the participant will be classified as disease progression confirmed (with an overall response of iCPD), as showing persistent unconfirmed disease progression (with an overall response of iUPD), or as showing disease stability or response (iRECIST-stable disease [iSD]/iRECIST-partial response [iPR]/iRECIST-complete response [iCR]).

Confirmation of Disease Progression

Disease progression is considered confirmed and the overall response will be iCPD, if any of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm compared to a prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST v1.1
- For new lesions, worsening is any of the following:
  - An increase in the new lesion sum of diameters by ≥5 mm compared to a prior iUPD time point
  - Visible growth of new nontarget lesions
  - The appearance of additional new lesions
- Progression in any other lesion category (ie, a category not driving the current iUPD) that would be defined as PD according to RECIST v1.1

Persistent iUPD

Disease progression is considered not confirmed and the overall response remains iUPD, if the both of the following occur:

- None of the previously identified factors confirming disease progression occur
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST v1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next scan in the regular imaging schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Disease progression is considered not confirmed and the overall response becomes iSD/iPR/iCR, if both of the following occur:

- None of the previously identified factors confirming disease progression occur
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold (by RECIST v1.1).

The response is classified as iSD or iPR depending on the sum of diameters of the target lesions, or, if all lesions resolve, as iCR.

In this case, the initial iUPD which was followed by response (iSD, iPR, or iCR) is considered to be disease pseudoprogression and the level of suspicion for disease progression is "reset." This means that the next scan that shows radiological disease progression, whenever it occurs, is again classified as iUPD by iRECIST and the confirmation process should be repeated before a response of iCPD can be assigned.

Management Following Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST and the participant continues to be clinically stable, study treatment may continue, and imaging should continue according to the regular on-study imaging schedule. If repeat imaging confirms PD per iRECIST (ie, iCPD), study treatment and regular imaging should be discontinued. However, if the participant is achieving a clinically meaningful benefit from study treatment, as assessed by the Investigator and confirmed by the GSK Medical Monitor, continuation of study treatment may be considered upon agreement of all parties. In this case tumor imaging should continue according to the regular on-study imaging schedule.

Detection of Disease Progression after Pseudoprogression Resolves

After resolution of disease pseudoprogression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time or after resolution of previous disease pseudoprogression. The nadir is always the smallest prior sum of diameters observed during the entire study, either before or after an instance of disease pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression doing so for the first-time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression and that progression has not resolved, iUPD results from any significant further growth of these nontarget lesions.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified "New Lesions – Target" show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified "New Lesions – Nontarget" show any significant growth

If any of the previously listed events occur this results in an overall response of iUPD and the iUPD evaluation process (see Assessment at Confirmatory Imaging) is repeated. Disease progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD with 1 exception as follows: If new lesions occurred at a prior instance of iUPD and the burden of new lesions has increased from its smallest value (the sum of diameters for "New Lesions – Target" has increased ≥5 mm from its nadir) at the confirmatory imaging, then iUPD cannot resolve to iSD or iPR; it will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR or until a confirmatory factor causes iCPD.

Response Criteria

Evaluation of Target Lesions

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

- **iSD, iPR, and iSD:** Equivalent to RECIST v1.1 stable disease (SD), partial response (PR), and complete response (CR), respectively, comparing target lesion sum of diameters to Baseline.
- **iUPD:** At least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum of diameters recorded on study (eg, percent change from nadir, where nadir is defined as the smallest sum of diameters recorded; this includes Baseline sum of diameters if that is the smallest on study). In addition, the sum must have an absolute increase from nadir of 5-mm. RECIST v1.1 PD is also considered the first iRECIST iUPD.
- **iCPD:** A further increase of ≥5 mm in sum of diameters compared to iUPD.

Evaluation of Nontarget Lesions

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

- **iCR and non-iCR/non-iPD:** Equivalent to RECIST v1.1 CR and non-CR/non-PD, respectively, comparing nontarget lesion sum of diameters to Baseline.
- **iUPD:** Unequivocal progression of existing nontarget lesions. RECIST v1.1 PD is also considered the first iRECIST iUPD
- **iCPD:** Any significant growth in lesions overall compared to iUPD. This does not have to meet the "unequivocal" standard of RECIST v1.1.

Evaluation of Overall Response

The following table (Table 15) presents the evaluation of overall response according to iRECIST at an individual time point for possible combinations of tumor responses in target and nontarget lesions, with or without new lesions, for participants with measurable (and nonmeasurable) disease at Baseline.

Table 15: Evaluation of Overall Response by iRECIST for Participants with Measurable Disease at Baseline

Target Lesions	Nontarget Lesions	New Lesions	Overall Response	
			No prior iUPD	Prior iUPD
iCR	iCR or NA	No	iCR	iCR
iCR	Non-iCR/Non-iUPD, NE, NA	No	iPR	iPR
iPR	iCR, Non-iCR/Non-iUPD, NE, NA	No	iPR	iPR
iSD	iCR, Non-iCR/Non-iUPD, NE, NA	No	iSD	iSD
iSD, iPR, iCR	iCR, Non-iCR/non-iUPD	Yes[1]	iUPD	iUPD if no increase in new lesions iCPD if new lesions increase in size or number
iSD, iPR, iCR	iUPD	No	iUPD	iUPD if no increase in nontarget lesions iCPD if nontarget lesions show further increase in size (does not have to be unequivocal)
iUPD	iUPD	No	iUPD	iUPD if no increase in target or nontarget lesions iCPD if target sum of diameters increases (≥5mm) or nontarget lesions increase (does not have to be unequivocal)
iUPD	iUPD	Yes[1]	NA	iUPD if no change in size or number of new lesions iCPD if new lesions increase in size or number
iUPD	iUPD	Yes[1]	iUPD	iUPD if no increase in target, nontarget, or new lesions iCPD if target sum of diameters increases (≥5mm), nontarget lesions increase (does not have to be unequivocal), or new lesions increase in size or number

Abbreviations: iCPD=iRECIST-confirmed progressive disease; iCR=iRECIST-complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors; iPR=iRECIST-partial response; iSD=iRECIST-stable disease; iUPD=iRECIST-unconfirmed progressive disease.

[1] Yes indicates a new lesion that was identified at a prior time point.

APPENDIX 3. Eastern Cooperative Oncology Group Performance Status

Table 16: ECOG Performance Status Grading

Description	Grade
Fully active, able to carry on all predisease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (ie, light housework, office work).	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead.	5

Source: (Oken, 1982)
Abbreviations: ECOG=Eastern Cooperative Oncology Group.

APPENDIX 4. Clinical Laboratory Tests

Screening-Only Testing

HIV and hepatitis B and C testing performed at Screening (or within 3 months prior to the first dose of study treatment) only; the following laboratory tests are performed:

- HIV-1 or HIV-2 antibodies
- Hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibodies

Continuous Laboratory Assessments

Parameters assessed throughout the study are listed in Table 17.

Table 17: Protocol-Required Safety Laboratory Tests

Laboratory Assessment	Parameters
Complete blood count (CBC)	• Differential white blood cell count • HCT • Hemoglobin • MCV • Platelet count • RBC or erythrocyte count • White blood cell count
Serum chemistry	• ALT • Albumin • ALP • Amylase (if not available, then lipase) • AST • Blood urea nitrogen (if not available, then urea) • Calcium • Chloride • Creatinine • GGT • Glucose • Lactate dehydrogenase • Magnesium • Phosphate • Potassium • Sodium • Total bilirubin • Total protein

Table 17 Protocol-Required Safety Laboratory Tests (Continued)

Laboratory Assessment	Parameters
Urinalysis	• Bilirubin • Glucose • Ketones • Leukocyte esterase (if not available, then leukocytes) • Microscopy (if clinically indicated) • Nitrite • Protein • Specific gravity
Thyroid panel	• TSH • T3 or FT3 • T4 or FT4 (or equivalent tests, where applicable)
Coagulation	• INR (ratio only) or PT (units: seconds) • aPTT (units:seconds) (coagulation will be collected if required due to an AE)
Pregnancy test	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)1
Other testing	• FSH • Estradiol (as needed in WONCBP only)

Abbreviations: AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; GGT=gamma-glutamyl transferase; hCG=human chorionic gonadotropin; Hct=Hematocrit; INR=international normalized ratio; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell count; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WONCBP=women of nonchildbearing potential.
[1] Post-Screening, local urine testing will be standard for the protocol, unless serum testing is required by local regulations or Institutional Review Board/Independent Ethics Committee.

APPENDIX 5. Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- The clinical trial is conducted in compliance with Clinical Trial Regulation EU 536/2014 (CTR Annex I 17(a)), trial result reporting (CTR Annex I 17(ai) and details on notifications (CTR Articles 52-54).
- All other applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually, or more frequently, in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/IEC of serious adverse events or other significant safety findings, as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of the United States Food and Drug Administration 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or their representative will explain the nature of the study, including the risk and benefits, to the participants or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participants or their legally authorized representative.
- A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date.
- GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study, understand the results of this study, learn more about the study treatment or about the study disease, publish the results of these research efforts, and/or work with government agencies or insurers to have the study treatment approved for medical use or approved for payment coverage.
- The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. Where approved by the IRB/IEC, the Investigator or authorized designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

Recruitment Strategy

- The study is planned to be conducted at sites in multiple countries. The recruitment plan will be defined by each participating site. Recruitment will be tracked using an electronic randomization system.

- The recruitment plan may be adapted based on the actual number of participants enrolled in each country. In case a site would fall behind in participant recruitment, a redistribution of the enrollment target per site in the participating countries may be made. This would allow the other participating sites to enroll additional participants to ensure full and timely enrollment of the overall targeted number of participants specified in this protocol.
- The procedures for participants identification/recruitment (e.g., referral letters, advertisements etc.) must be approved by the IRB/IEC together with the material intended for participants identification/recruitment and participants use.
- Multiple Healthcare Provider materials are available for use along with participant infographics to summarize the study.

Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that his or her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his or her data to be used as described in the informed consent.
- The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

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Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the Source Data Agreement.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Source data are shared with third parties contracted by GSK for external assessment or adjudication (e.g. endpoint adjudication committee; expert reader). The non-exhaustive list of source data shared may include [discharge summaries, imaging reports, scans, videos, pathology reports, biological specimens, ECG reports, etc.]. Participant names or any information that would make the participant identifiable or is not essential for the external assessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open, the date of which will be the study start date.

Study/Site Termination

GSK or designee reserves the right to close the study site or terminate the study at any time for any reason, at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to the following:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, and/or GCP guidelines
- Inadequate or no recruitment of participants (evaluated after a reasonable amount of time) by the Investigator
- Total number of participants included earlier than expected
- If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

APPENDIX 6. Contraceptive and Barrier Guidance

CCI [redacted]

However, blockade of T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) and programmed cell death-ligand 1 signaling in murine models of allogeneic pregnancy can eliminate fetomaternal tolerance and cause spontaneous abortion, as indicated by an increase in embryo resorption and a reduction in litter size, and TIM-3 down-regulation has been correlated with human miscarriage (D'Addio, 2011; Wang 2015a; Wang, 2015b).

Therefore, female participants may only be enrolled if they are women of childbearing potential (WOCBP) (see WOCBP definition) who are nonpregnant, nonbreastfeeding and are willing to use 1 highly effective form of contraception (Table 18), or are considered women of nonchildbearing potential (WONCBP) (see WONCBP definition). Male participants may only be enrolled if they agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception, as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential who is not currently pregnant, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

Participants should be informed that taking the study medication may involve unknown risks to a fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, they must adhere to the study contraception requirements for the duration of the study and through at least CCI [redacted] after the last study treatment. (Note: Duration of contraceptive use after the last dose of docetaxel must be consistent with local requirements and the local approved product label; however, the minimum duration is CCI [redacted] after the last dose of docetaxel). If there is any question that a participant will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

If instructed in the local label, the Investigator should advise fertile male participants receiving docetaxel to consider collecting and storing viable sperm prior to undergoing treatment given that docetaxel has genotoxic effects and may alter male fertility.

Table 18: Female Contraceptives Allowed During the Study

FEMALE CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective[2] Methods that Have Low User Dependency *(Failure rate of <1% per year when used consistently and correctly)*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[3]
• IUD
• IUS3
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) – Azoospermia is a highly effective contraceptive method, provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, then an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective[2] Methods that Are User Dependent *(Failure rate of <1% per year when used consistently and correctly)*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation3 – oral – intravaginal – transdermal – injectable (not an option for participants in certain countries, including Germany)
• Progestogen-only hormone contraception associated with inhibition of ovulation3 – oral – injectable

Table 18: Female Contraceptives Allowed During the Study (Continued)

FEMALE CONTRACEPTIVES[1] ALLOWED DURING THE STUDY INCLUDE THE FOLLOWING:
Highly Effective[2] Methods that Are User Dependent (Continued) (*Failure rate of <1% per year when used consistently and correctly)*
• Sexual abstinence – Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant. Periodic abstinence (calendar, symptom-thermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are **not acceptable** methods of contraception.

Abbreviations: CTFG=Clinical Trial Facilitation Group; IUD=intrauterine device; IUS=intrauterine hormone-releasing system.

[1] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[2] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[3] Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with CTFG guidelines, then acceptable contraceptive methods are limited to those that inhibit ovulation as the primary mode of action. Male condoms and female condoms should not be used together (due to risk of failure from friction).

Definition of WOCBP

Women in the following categories are considered **WOCBP** (fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile

Definition of WONCPB

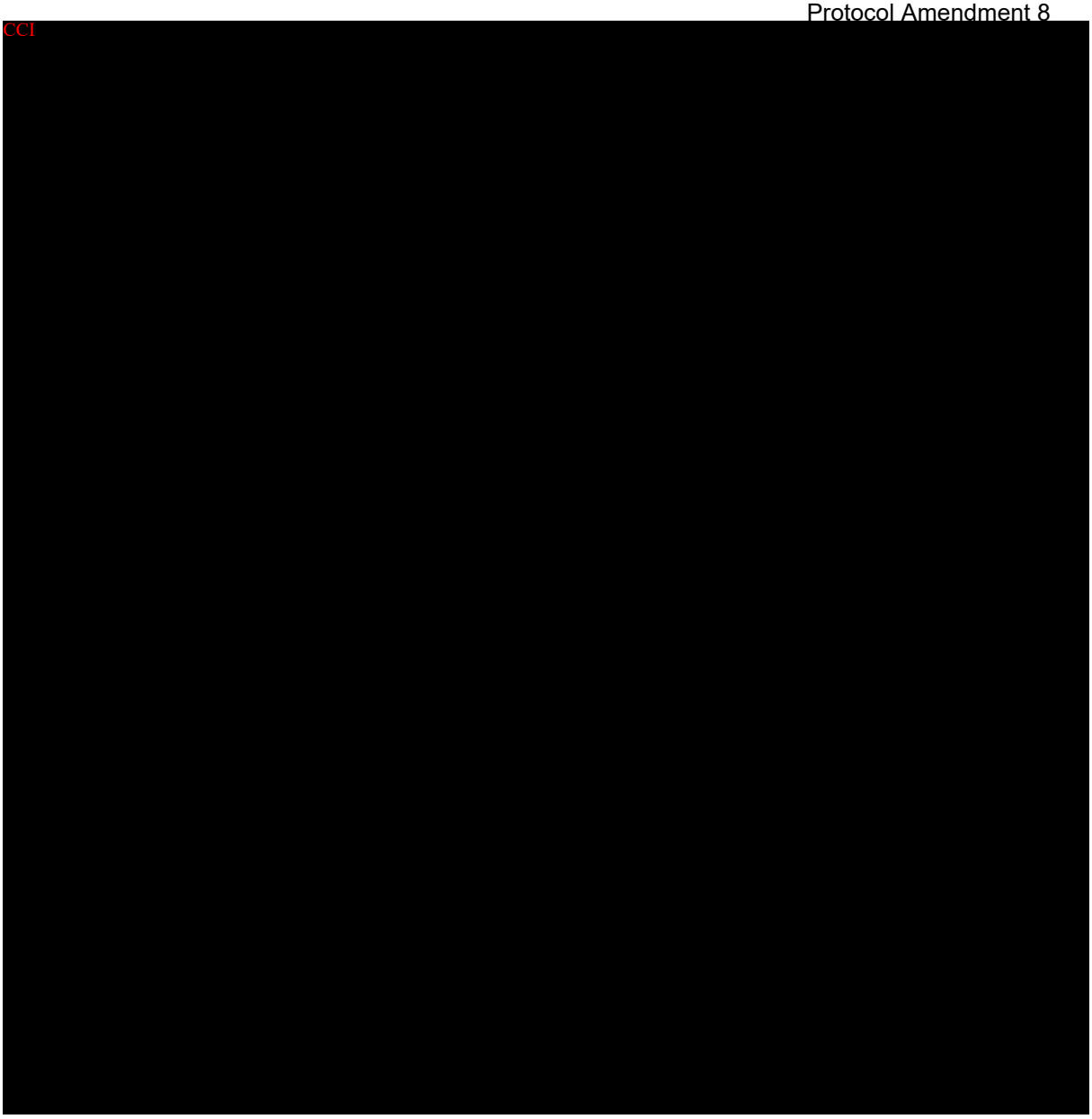
Women in the following categories are considered **WONCBP** (not fertile):

1. Premenopausal female with permanent infertility due to 1 of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy
2. Postmenopausal female

Note the following:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- For individuals with permanent infertility due to an alternate medical cause other than those previously listed, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied when determining study entry.
- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study treatment, an additional evaluation should be considered.
- Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

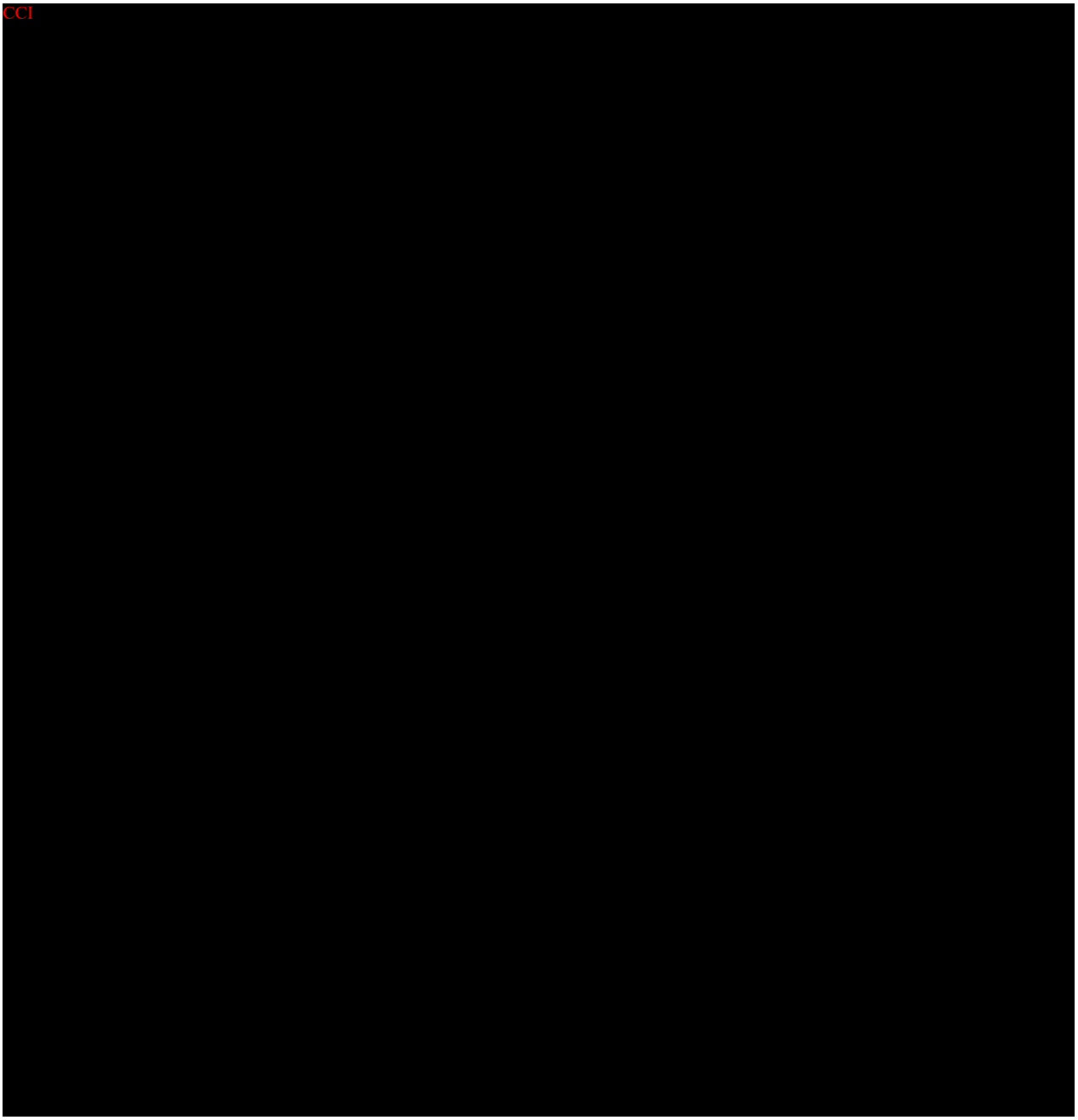
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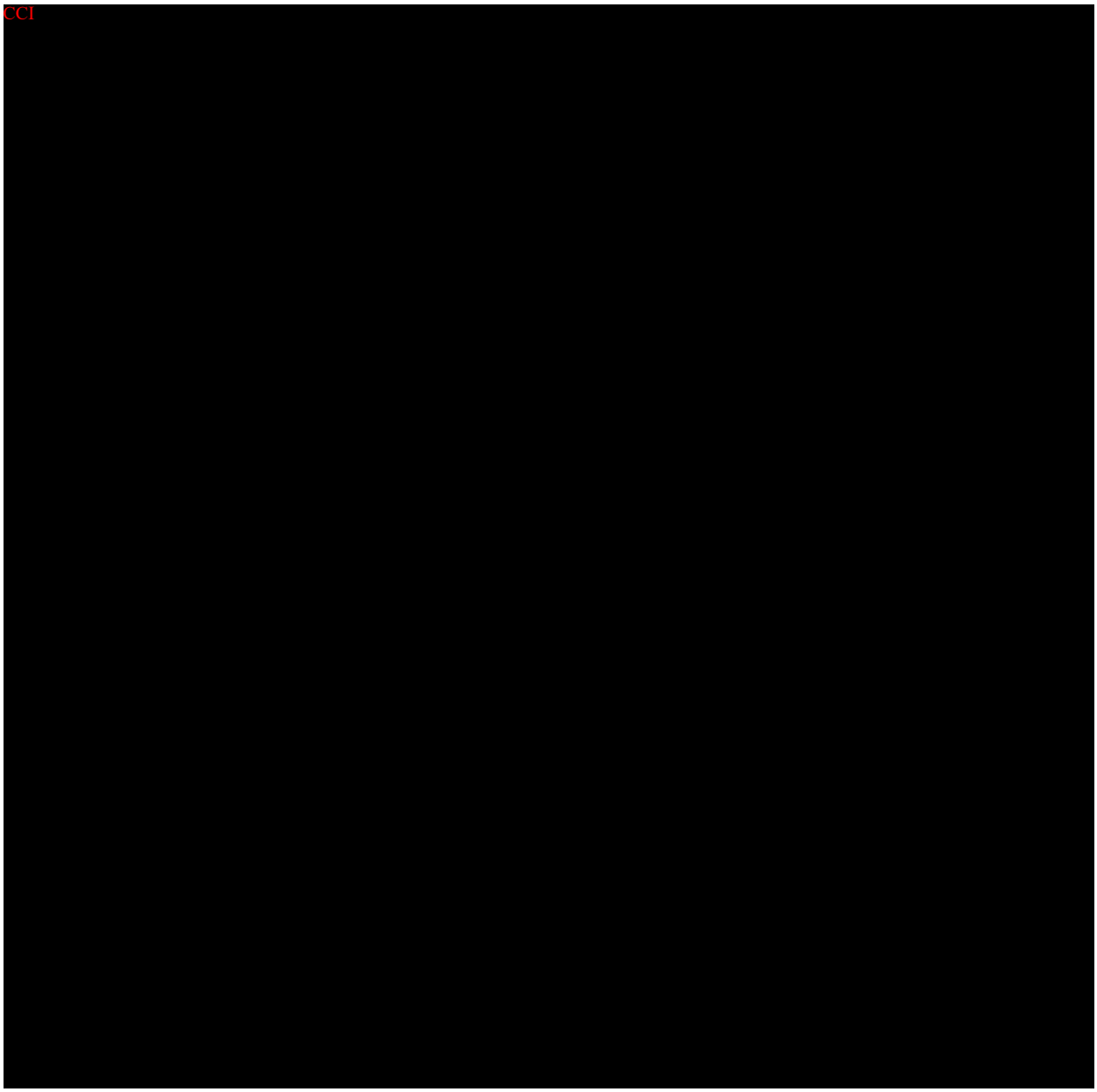
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APPENDIX 10. Adverse Events, Serious Adverse Events, and Special Situations: Definitions and Procedures for Recording, Follow-up, Evaluating, and Reporting

Definitions and Criteria

Definition of an Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, and vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including an increase in either frequency or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.

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

Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the following criteria:

- **Results in death**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**

- **Other situations**
  - Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment of allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

Definition of a TEAE

A treatment-emergent adverse event (TEAE) is any event that was not present prior to the initiation of study treatment or any event already present that worsens in either intensity or frequency following exposure to study treatment.

Definition of Cardiovascular Events

Investigators will be required to fill out the specific cardiovascular event page of the electronic case report form (eCRF) for the following AEs and SAEs, which are considered cardiovascular events:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Recording and Follow-up of AEs and SAEs

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK required form.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Expectedness

Expectedness (whether an AE is "expected" or "unexpected") will be determined by the Sponsor. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information provided in the Reference Safety Information for dostarlimab and cobolimab in the Investigator's Brochures (IBs) and for docetaxel in the prescribing information.

Assessment of Intensity

Investigators should assess the severity of AEs according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0. In general, NCI-CTCAE severity grades are as follows:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; easily tolerated
- **Grade 2:** Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs) (instrumental ADLs refer to preparing meals, shopping for groceries or clothes, using the telephone, or managing money)
- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADLs (self-care ADLs refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and being not bedridden)
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death related to AE

A distinction should be made between **serious** and **severe** AEs. Severity is a measure of intensity, whereas seriousness is defined by the previously stated criteria. For example, a mild degree of gastrointestinal bleeding requiring an overnight hospitalization for monitoring purposes may be considered an SAE but is not necessarily severe. Similarly, an AE that is severe in intensity is not necessarily an SAE. For example, alopecia may be assessed as severe in intensity but may not be considered an SAE.

Assessment of Causality

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. One of the following categories should be selected based on medical judgment, considering all contributing factors:

- **Related:** A causal relationship between the medicinal product (or study procedures) and AE is a reasonable possibility. For example, the occurrence of the AE cannot be explained by other causative factors. The AE, however, can be explained by the pharmacological effect of the medicinal product such as a similar event having been reported previously, alteration of the dose effect, or the timing or seriousness of the AE. Positive rechallenge/dechallenge is supportive.
- **Not related:** A causal relationship between the medicinal product (or study procedures) and AE is not a reasonable possibility; there is no temporal relationship between the medicinal product and the event, or an alternative etiology is more reasonable.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to GSK. However, **it is very important that the Investigator always assesses causality for every event before the initial transmission of the SAE data to GSK.**
- The Investigator may change his/her opinion of causality in light of follow-up information and may send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Reporting of SAEs to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the GSK Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the Study Reference Manual.

SAE Reporting to GSK via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK Medical Monitor or the SAE coordinator.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Study Reference Manual.

CCI

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APPENDIX 12. Abbreviations and Trademarks

The following abbreviations and specialist terms are used in this study protocol:

Table 22: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADA	antidrug antibody
ADL	activity of daily living
AE	adverse event
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BICR	blinded independent central review
BOR	best overall response
CD	cluster of differentiation
CD8 T	CD8+ cytotoxic T (cells)
CFR	Code of Federal Regulations
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CoV-2	coronavirus 2
COVID-19	Coronavirus Disease 2019
CPMS	Clinical Pharmacology Modeling and Simulation
cCR	confirmed complete response
cPR	confirmed partial response
CR	complete response
CRO	contract research organization
CT	computed tomography

Abbreviation or Specialist Term	Explanation
CTLA-4	cytotoxic T lymphocyte-associated protein 4
CV	coefficient of variation
CYP3A4	cytochrome P450 3A4 enzyme
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DOR	duration of response
DRE	disease-related event
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ED	Early discontinuation
EGFR	epidermal growth factor receptor
CCI [redacted]	
EOT	End-of-Treatment
EQ-5D-3L	European Quality of Life 5 Dimensions 3 Level Scale
FACT-GP	Functional Assessment of Cancer Therapy-General Population
EoMS	End of Main Study
EoS	End of Study
FACT-GP5	Functional Assessment of Cancer Therapy-General Population 5-category Response Scale
FDA	United States Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography

Abbreviation or Specialist Term	Explanation
FFPE	formalin-fixed paraffin-embedded
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GSK	GlaxoSmithKline
HR	hazard ratio
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HRU	healthcare resource use
IA	interim analysis
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	informed consent form
iCPD	iRECIST-confirmed progressive disease
iCR	iRECIST-complete response
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL-2	interleukin-2
IFN-γ	interferon-gamma
IO	Immuno-oncology
IP	Investigational product
iPR	iRECIST-partial response
imAE	immune-mediated adverse event

Abbreviation or Specialist Term	Explanation
IRB	Institutional Review Board
iRECIST	modified Response Evaluation Criteria in Solid Tumors v1.1 for immunotherapies
iSD	iRECIST-stable disease
ITT	intent-to-treat (population)
iUPD	iRECIST-confirmed progressive disease
IV	intravenous
IVD	in vitro companion diagnostic device
KM	Kaplan-Meier
LAG-3	lymphocyte-activation gene 3
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
NSCLC-SAQ	Non-Small Cell Lung Cancer-Symptom Assessment Questionnaire
OF	O'Brien Fleming
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1

Abbreviation or Specialist Term	Explanation
PD-L2	programmed death-ligand 2
PET	positron emission tomography
PFS	progression-free survival
CCI	[redacted]
PK	pharmacokinetic(s)
PP	per-protocol (population)
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-reported Outcomes Version of the Common Term Criteria for Adverse Events
QTc	corrected QT interval
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QTL	quality tolerance limit
QxW	every x (eg, 2, 3, 6) weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RO	receptor occupancy
ROS1	c-ros oncogene 1
SAE	serious adverse event
SAF	safety (population)
SAP	Statistical Analysis Plan
SARS	severe acute respiratory virus
SD	stable disease

Abbreviation or Specialist Term	Explanation
CCI	[redacted]
SoA	schedule of activities
SRM	Study Reference Manual
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TIM-3	T-cell immunoglobulin and mucin-domain containing-3
TPS	tumor proportion score
TNFα	tumor necrosis factor alpha
TTD	time to deterioration
ULN	upper limit of normal
US	United States
WOCBP	woman of childbearing potential
WONCBP	woman of nonchildbearing potential

The following trademarks are used in this study protocol:

Table 23 Trademark Information

Trademarks of the GlaxoSmithKline group of companies
JEMPERLI™

Trademarks not owned by the GlaxoSmithKline group of companies
CYRAMZA
KEYTRUDA
MedDRA
PRO-CTCAE

APPENDIX 13. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 07 (20 December 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment

Amendment 07 is a global protocol amendment created primarily to update the CCI [redacted]

A table of key changes from Protocol Amendment 6 to Amendment 7 is shown below:

Summary of Changes for the Amendment

Table 24 Summary of Changes for Amendment 7

Section(s) Affected	Description of Change	Brief Rationale
Title page	Updated the Sponsor address as follows: GSK Research & Development Limited 79 New Oxford Street London WC1A 1DG UK	To align with the Sponsor's legal requirement.
CCI [redacted]		
Appendix 5	Added a sentence for EU-CTR compliance. • The clinical trial is conducted in compliance with Clinical Trial Regulation EU 536/2014 (CTR Annex I 17(a)), trial result reporting (CTR Annex I 17(ai) and details on notifications (CTR Articles 52-54).	To comply with EU-CTR regulation.

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Throughout	Changed the “immune-related adverse event (irAE)” to “immune-mediated adverse event (imAE)”.	To update the document in accordance with FDA guidance.

Amendment 06 (24 July 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment

Amendment 06 is a global protocol amendment created primarily to update the statistical section to reflect the updated statistical assumptions and testing procedure.

A table of key changes from Protocol Amendment 5 to Amendment 6 is shown below:

Summary of Changes for the Amendment

Table 25: Summary of Changes for Amendment 06

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Table 3. Schedule of Activities for Study 213410	CCI [redacted]	
Section 6.1 Table 9	NIMP and footnote 1 were removed from the docetaxel column of Table 9 Study Treatments for Study 213410	Docetaxel has always been used in the context of the study, in accordance with regulation as an investigation medicinal product (IMP) and all necessary reporting, safety assessments and submissions has been made from study inception, treating docetaxel as investigational. The update is to correct this in the protocol.
Section 6.1.3.	Language added for docetaxel total dose calculations to allow variation between the actual dose vs the calculated dose of docetaxel given for all participants.	Per local practice guidelines, some sites are not using the participant's BSA at each visit to calculate the docetaxel dose administered for that visit but using alternative methods e.g. not accounting for weight fluctuations, dose banding or dose capping. Including this language in the protocol accommodates current local practiced methods used for docetaxel dosing.
Table 11. Infusion Reaction Treatment Guidelines	Language added for continuation of a lower infusion rate of drug administration following a reduction of the infusion rate for an infusion reaction.	To mitigate further infusion reactions following an initial infusion reaction that required a reduction in the infusion rate of drug administration.

Section(s) Affected	Description of Change	Brief Rationale
Section 7.2	CCI [redacted]	
Section 8.1.1 Table 13		
Section 8.8		
Section 9.2 and Section 9.4.3		
Section 9.3.2 and Section 9.4.3		
Appendix 1	CCI [redacted]	To allow for 2 scans to assess whether disease is stable
Section 1.1, Section 1.3, Section 4.1, Section 4.4, Section 6.7, and Section 8.5.1.	Updates to comply with protocol template	To comply with protocol template

Section(s) Affected	Description of Change	Brief Rationale
Appendix 4	Removal of blood from laboratory assessments required for urinalysis	The blood analyte is not available in Veeva Standard Master Library on Urinalysis eCRF, as a result this analyte field cannot be added into Study eCRF page. As such it was removed from the eCRF. This update was to ensure consistency with data collection in the eCRF.
	Updates to comply with protocol template	To comply with protocol template
	Minor editorial corrections	To correct minor editorial errors
	Headers and title page were updated with new document number and amendment information; Protocol Amendment Summary of Changes section was updated to include rationale for this amendment; minor corrections and formatting adjustments, and to add clarification and/or remove discrepancies.	Editorial changes as needed.

Amendment 05 (11 August 2023)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment

Amendment 05 is a global protocol amendment created to primarily remove Interim analysis 2 (IA-2) and to comply with EU-CTR template requirements. A description and rationale for all changes is provided in Table 26.

Summary of Changes for the Amendment

Table 26 Summary of Changes for Amendment 05

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, and Appendix 13. Protocol Amendment History	Headers and cover page were updated with new version number; Protocol Amendment Summary of Changes section was updated; information for Amendment 04 moved to Appendix 13 and replaced with Amendment 05 (current amendment) information.	Editorial changes to align with the Sponsor's standard protocol template and ways of working.
Throughout	Administrative updates to add clarification, cross-references, updates to abbreviations and/or remove discrepancies.	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error correction.
CCI [redacted]		
Section 1.1, Section 1.3 Schedule of activities Table 3, Section 4.1,	Removed mention of the GSK Study 213299. Removed section 4.5	GSK Study 213299 terminated.
Section 1.3 Schedule of activities	CCI [redacted]	
Section 1.1 Synopsis Section 4.1, Section 5.1, Section 8.2.3, Section 8.6.1, Section 8.6.2	Updated details of theCCI [redacted]	Reference to study reference manual (SRM) provided.
Section 4.2.1 Participant input into design	Section added to comply with EU-CTR template.	To fulfil EU-CTR template requirement.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Schedule of activities Table 3	Modified follow up and post-treatment follow up crosslinked to relevant sections with footnotes. If a participant is not dosed, any assessment completed should be recorded as an unscheduled visit. Coagulation information will also be collected, if required, due to occurrence of a liver event. Clarified optional blood sample collection timepoint (C1D1) for genetic testing. Clarification in notes that all concomitant medications will be collected from the start of study treatment until 90 days after the last dose of study treatment or until the participant starts alternate anticancer therapy, whichever occurs first. In tumor assessments, a baseline brain scan is mandatory. Clarified that survival assessment is via a phone call check-in. OS follow up is mandatory for all randomized subjects including patients randomized and not treated.	Clarifications to site.
Section 1.3 Schedule of activities, Section 6.9	Prophylactic G-CSF is strongly recommended to avoid neutropenia complications due to chemotherapy.	Recommendation of a concomitant medication.
Section 1.3 Schedule of activities	Addition of Thyroid panel testing at 30 (±7) days and 90 (±7) days after last dose.	Added as per feedback from Swedish regulatory authority.

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3 Schedule of activities Table 4	90 day visit is a safety follow-up visit.	Correction.
Section 1.3 Schedule of activities Table 4, Table 5 Section 8.7 and 8.8	CCI [redacted]	Clarifications and corrections to site.
Section 1.3 Schedule of activities Table 4, Table 5		Clarifications and corrections to site.
Section 1.1, 1.3 Schedule of activities Table 5 Section 4.1 and 8.6.1		Clarification to site.
Section 2.2 Background	Updated with more recently available NSCLC epidemiological data, and safety data from AMBER study available in Cobolimab IB v6.	Recent background information.
Section 4.1 Overall design	CCI [redacted]	

Section(s) Affected	Description of Change	Brief Rationale
Section 6.1.1 Cobolimab	Revision of information regarding measurement of vial for administration of Cobolimab.	Clarification to site.
Section 6.4.1.2 Dose Levels and Dose Adjustment	Revision of guidelines and recommendations to investigator for Docetaxel dose reduction and dose delay.	Clarification to site.
Section 6.4.2.1 Management of IO-Related AEs Table 10 Section 6.4.2.2. Management of Chemotherapy-Related AEs	If IO treatment is delayed, docetaxel should also be delayed. If IO treatment is discontinued for irAEs, docetaxel should also be discontinued.	Clarifications to site.
Section 6.7.1 Protocol-Defined Overdose	CCI [redacted]	
Section 7.1 Discontinuation of Study Treatment Section 7.2 Participant Discontinuation/Withdrawal from the Study		
Section 7.1.1 Liver Chemistry Stopping Criteria (Figure 2) Appendix 7: Table 21-23		
Section 8.1 General Guidelines	Mandatory text added on the rationale for collection of sex, race and ethnicity data.	Template mandatory text.
Section 8.1.1 Table 13	CCI [redacted]	Correction.

Section(s) Affected	Description of Change	Brief Rationale
Section 8.2.2 Baseline Documentation of Target and Nontarget Lesions	Brain lesions should be imaged at every scheduled imaging visit for patients with brain metastasis.	Clarifications to site.
Section 9.3.2 Interim Analysis	Added end of study analysis.	Clarification of planned analyses.
Section 9.4.7 Exploratory PK Analyses	Early data access to designated representatives. Removal of the text regarding responsibility of PK analyses by CPMS.	Wording added to support planned analyses, and clarifications to site.
APPENDIX 4 Clinical laboratory tests Table 14	Units for coagulation have been added.	Clarifications to site.
APPENDIX 5 Regulatory ethical, and study oversight considerations	Revisions to incorporate recruitment strategy, conditions for study site termination, and mandatory text related to data protection, and dissemination of clinical study data. Reference to SRM has been revised to source data agreement.	To fulfil EU-CTR template requirement. Clarification to site.
APPENDIX 11 Country specific requirements	Revised France requirements added.	Updated language added.

Amendment 04 (06 October 2021)

Overall Rationale for the Amendment

Amendment 04 was a global protocol amendment created in response to Health Authority feedback to provide clarifications to the protocol, including those that impact participant enrollment and site conduct. A description and rationale for all changes is provided in Table 27.

Summary of Changes for the Amendment

Table 27: Summary of Changes for Amendment 04

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, Protocol Amendment Summary of Changes, and Appendix 13. Protocol Amendment History	Headers and cover page were updated with new version number; Protocol Amendment Summary of Changes section was updated; information for Amendment 03 moved to Appendix 13 and replaced with Amendment 04 (current amendment) information	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error correction

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1 Synopsis (Treatment Groups and Duration) Section 1.3. Schedule of Activities (Table 3: Schedule of Activities for Study 213410, Treatment Administration rows) Section 4.1. Overall Design Section 6.1.3. Docetaxel	Clarified that docetaxel infusion time (60 minutes) is based on the product label and that institutional discretion on this parameter is not allowed.	Sites must follow the product label when infusing docetaxel
Section 1.1. Synopsis (Overall Design) Section 4.1. Overall Design	Added/clarified information regarding the planned enrollment pause during IA-1	Per Heath Authority request
Section 1.1. Synopsis (Overall Design) Section 4.1. Overall Design Section 5.1. Inclusion Criteria (criterion 7) Section 8.2.3 Determination of PD-L1 Status Prior to Randomization Section 8.6.1. Biomarker Sample Collection Section 8.6.2. Tumor Tissue Biomarker Analysis	Updated participant eligibility criteria and guidelines relating to PD-L1 status stratification factor: PD-L1 status by the CCI [redacted] CCI [redacted] CCI [redacted] is required for participation; if a prior result is not available at Screening, the participant must submit archival or fresh tumor tissue to be tested by 1 of these methods (locally or centrally, as available) and results must be available prior to randomization.	To accommodate different local testing practices for PD-L1 status and reduce enrollment time for participants

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Overall Design) Section 5.1. Inclusion Criteria (criteria 2 and 3)	Criterion 2: Clarified that only participants with squamous or nonsquamous cell carcinoma are eligible Criterion 3: Clarified that prior therapy received by a participant must only include a platinum-based doublet chemotherapy regimen and an anti-PD-1 or anti-PD-L1 antibody; no other biologic alone or in combination is allowed and novel combinations are not allowed. Participants previously treated with targeted therapies, including angiogenesis inhibitors (eg, bevacizumab, ramucirumab, lenvatinib), are not eligible.	Clarification to further specify intended study population
Section 1.3. Schedule of Activities (Table 3: Schedule of Activities for Study 213410, Thyroid panel row) Section 1.3. Schedule of Activities (Table 3: Schedule of Activities for Study 213410, Treatment Administration rows)	Revised thyroid testing frequency to Q6W following testing at C1 instead of Q6W following testing at C1 and C6. Clarified that postinfusion monitoring will be done per institutional practice.	Error correction and per Health Authority feedback to conduct thyroid panel more frequently per ESMO guidelines. Clarification requested by Health Authority.

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities (Table 5: Sampling Schedule for Biomarker Analysis for Study 213410) Section 4.1. Overall Design Section 5.1. Inclusion Criteria (criterion 6) Section 8.6.1. Biomarker Sample Collection	Removed definition of freshly cut slides ("<90 days from the date of sectioning") for the required tumor tissue sample	This information is captured in other study documentation such as the Study Reference Manual and is not needed in the protocol
Section 2.2.4. Rationale for Studying Immuno-Oncology Therapy Combinations and Immuno-Oncology Therapies in Combination with Chemotherapy in NSCLC Appendix 11. Abbreviations and Trademarks (Table 25: Trademark Information)	Added approval information and reference to label for dostarlimab (JEMPERLI)	Dostarlimab (JEMPERLI) is now an approved and marketed product for the treatment of certain cancers
Section 2.3.1. Risk Assessment (Table 6: Risk Assessment for Study 213410, irAEs row)	Clarified that any toxicity (not just Grade 3) related to prior immunotherapy leading to study treatment discontinuation makes a participant ineligible for the study (in alignment with exclusion criterion 1)	Correction
Section 5.1. Inclusion Criteria (criterion 3a)	Clarified that a PD-1 or PD-L1 antibody received during a previous clinical study counts as a prior line of therapy if the antibody has been approved for an indication in at least 1 country	Clarification

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 5.1. Inclusion Criteria (criterion 12a for male contraception) Appendix 6. Contraceptive and Barrier Guidance	Added instructions for the Investigator to discuss storage of viable sperm for fertile male participants receiving docetaxel prior to treatment as docetaxel has genotoxic effects and may alter male fertility where advised by the local label	Per Health Authority feedback to align with local approved product label for docetaxel
Section 5.2. Exclusion Criteria (criterion 7)	Specified that participants with ALT >2.5×ULN are not eligible	Clarification
Section 5.2. Exclusion Criteria (criterion 12)	Clarified that hepatitis C virus RNA testing can be used to determine participant eligibility	Participants must have a negative hepatitis C antibody test result in the absence of an RNA test for hepatitis C virus; if a confirmatory RNA test is available, a positive test result will exclude a participant, while a negative test result (indicating absence of active infection) will allow the participant to enter into the study
Section 5.2. Exclusion Criteria (criterion 15) Section 6.9.1. Prohibited Medications and Nondrug Therapies	CCI [redacted]	Clarification on steroid use eligibility requirements
Section 5.2. Exclusion Criteria (criterion 22) Section 6.9. Concomitant Medications and Nondrug Therapies	Added language regarding the use of COVID-19 vaccines in this study	The use of authorized COVID-19 vaccines is allowed for participants in this study

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 5.2. Exclusion Criteria (criterion 25)	Specified that the only anticipated surgical procedure requiring interruption of aspirin or other nonsteroidal anti-inflammatory drugs on the study is a biopsy procedure for participants who do not have an archival biopsy	Clarification
Section 5.2. Exclusion Criteria (note and cross-reference added) Appendix 11. Country-Specific Requirements (new appendix for UK-specific exclusion criteria)	CCI [redacted]	

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 7.1. Discontinuation of Study Treatment	Clarified that the study cannot be closed while there are still participants deriving clinical benefit from ongoing study treatment (and likewise that treatment would not be discontinued if the study is closed or terminated), in line with the end of study definition Clarified that study treatment must be discontinued in the case of withdrawal of participant, consent, the participant is lost to follow-up, it is in the best interest of the participant as judged by the Investigator and/or Sponsor, and the participant becoming pregnant	Clarification per Health Authority request Revised per Health Authority feedback that these situations must warrant study treatment discontinuation

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 7.2. Participant Discontinuation/Withdrawal from the Study	Clarified that if a participant requests destruction of any samples taken and not tested, the samples will be destroyed	Revised per Health Authority feedback that not only will the request for sample destruction be recorded, but the samples will also be destroyed, accordingly
CCI [redacted]		
Section 9.4.6. Exploratory Efficacy Analyses	Clarified that analyses of endpoints using iRECIST criteria apply to Arms A and B only	iRECIST data is captured for all participants, however, formal analyses will only be conducted for participants in Arms A and B, who are receiving immunotherapy (cobolimab and/or dostarlimab)

Table 27: Summary of Changes for Amendment 04 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Appendix 4. Clinical Laboratory Tests (Table 19: Protocol-Required Safety Laboratory Tests; Serum chemistry row) Appendix 4. Clinical Laboratory Tests (Table 19: Protocol-Required Safety Laboratory Tests; Urinalysis row)	Added that lipase may be measured as part of serum chemistry when amylase testing is not available Added that leukocytes may be measured as part of urinalysis when leukocyte esterase testing is not available	To accommodate differences in local laboratory practices
Appendix 5. Regulatory, Ethical, and Study Oversight Considerations (Committees Structure)	Added high level details regarding the IDMC	Per Health Authority request to address the IDMC meeting frequency, format, and responsibility
CCI [redacted]		

Abbreviations: ADA=antidrug antibody; AE=adverse event; ALT=alanine aminotransferase; C=Cycle; COVID-19=Coronavirus Disease 2019; DRESS=drug reaction with eosinophilia and systemic symptoms; ESMO=European Society for Medical Oncology; GSK-GlaxoSmithKline; IA=interim analysis; IDMC=independent data monitoring committee; INR=international normalized ratio; IO=immuno-therapy; irAE=immune-related adverse event; irAR=immune-related adverse reaction; iRECIST= modified Response Evaluation Criteria in Solid Tumors; LDT=laboratory developed test; NSCLC=non-small cell lung cancer; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1; Q6W=every 6 weeks; CCI [redacted] TTD=time to deterioration; UK=United Kingdom.

Amendment 03 (22 December 2020)

Overall Rationale for the Amendment

Amendment 03 was a global protocol amendment created in response to Health Authority feedback to provide clarifications to the protocol and to update the stratification factors used in the study. A description and rationale for all changes is provided in Table 28.

Summary of Changes for the Amendment

Table 28: Summary of Changes for Amendment 03

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; Protocol Amendment Summary of Changes section was updated	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Throughout	Administrative updates to add clarification and/or remove discrepancies	Editorial changes were made for accuracy, clarity, conformity, flow, and typographical error correction

Table 28: Summary of Changes for Amendment 03 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Overall Design) 1.2 Schema/Figure 1: Schema for Study 213410 Section 1.3. Schedule of Activities/Table 3: Schedule of Activities for Study 213410 Section 4.1. Overall Design Section 5.1. Inclusion Criteria (criterion 7, new) Section 6.3.1. Method of Treatment Assignment – Randomization Section 8.2.3 Determination of PD-L1 Status Prior to Randomization (new) 8.6.1. Biomarker Sample Collection 8.6.2. Tumor Tissue Biomarker Analysis	Added PD-L1 status (TPS≥50% vs TPS <50%) as a third stratification factor and modified existing prior lines of therapy stratification factor from, " IO + chemotherapy vs IO followed by chemotherapy," to, "1 prior line vs 2 prior lines." Added participant eligibility criteria and guidelines relating to new PD-L1 status stratification factor: PD-L1 status by the CCI [redacted] is required for participation; if a prior result is not available at Screening, the participant must submit archival or fresh tumor tissue to be tested by the assay (locally or centrally, as available) and results must be available prior to randomization.	Requested change per Health Authority feedback
Section 1.1. Synopsis (Overall Design) Section 5.2. Exclusion Criteria (criterion 3)	Restricted exclusion criteria regarding driver mutations to EGFR, ALK, and ROS-1 only and clarified that participants with unknown status for these mutations are not eligible (previously allowed) and participants with squamous histology need not be tested for these driver mutations	Program update and correction to previous text that indicated participants with unknown driver mutation status are eligible for this study

Table 28: Summary of Changes for Amendment 03 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.1. Synopsis (Treatment Groups and Duration) Section 1.3. Schedule of Activities/Table 3: Schedule of Activities for Study 213410 Section 4.1. Overall Design	Clarified that the Post-treatment Follow-up visits occur every 90 (±14) days from the 90-day Safety Follow-up Visit, not every 90 (±14) days after the last dose	Error correction
Section 1.1. Synopsis (Treatment Groups and Duration) Section 1.3. Schedule of Activities/Table 3: Schedule of Activities for Study 213410 Section 4.1. Overall Design Section 6.1.3. Docetaxel	Clarified that docetaxel should be administered until disease progression or unacceptable toxicity “or” (not “and”) according to local practice and the local approved product label. Removed additional redundant language regarding the discontinuation of docetaxel according to the local regulatory authority and Investigator’s discretion.	Clarification
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities for Study 213410	Clarified that randomization may occur up to 3 days before Day 1, not any time between Screening and Cycle 1/Day 1	Error correction

Table 28: Summary of Changes for Amendment 03 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities/Table 3: Schedule of Activities for Study 213410 Section 8.4.5. Clinical Safety Laboratory Assessments Section 8.5. AEs, SAEs, and Other Safety Reporting (including Table 14: Collecting and Reporting AEs, Pregnancy, and Survival) Section 9.4.5.2. AEs Appendix 10. Adverse Events, Serious Adverse Events, and Special Situations: Definitions and Procedures for Recording, Follow-Up, Evaluating, and Reporting Section 8.5.8. Adverse Events of Special Interest (new section)	Removed references to AESI collection Added the AESIs for dostarlimab and cobolimab	AESIs have been defined in the protocol. However, there are not specific eCRFs as they will be defined programmatically by the Sponsor. Based on mechanism of action, immune-related events and infusion-related reactions have been defined as AESIs for both dostarlimab and cobolimab
Section 1.1. Synopsis (Treatment Groups and Duration) Section 1.3. Schedule of Activities/Table 3: Schedule of Activities for Study 213410 Section 4.1. Overall Design Section 4.5. Screening under Molecular Disease Characterization Initiative Study 213299 (new section)	Added a new section (4.5) to provide details pertaining to participants who may already be enrolled in GSK Study 213299 (molecular disease characterization study) that may not need to undergo repeated screening procedures for this study (213410) Added a note in the Schedule of Activities pointing to this new section as it could impact screening procedures for this study	Molecular disease characterization study 213299 is a nontherapeutic GSK study that may refer participants to this study (213410)

Table 28: Summary of Changes for Amendment 03 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		Clarification
Section 5.2. Exclusion Criteria (criterion 25)	Clarified that the eligibility criteria requiring a participant to interrupt aspirin for a 5-day period is due to the anticipation of surgical procedures such as biopsies	Clarification
Section 6.4.2.1. Management of IO-Related AEs/Table 10: Dose Modification Guidelines for irAEs	Instructions for IO-related dose modifications updated	Revisions to ensure that information is consistent with the product information for the study treatments used in the protocol
Section 6.9.1. Prohibited Medications and Nondrug Therapies	Added description of possible exceptions to prohibition of radiotherapy while a participant is receiving study treatment	Clarification
Section 8.1.1. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic/Table 13: Critical Data Collection and Safety Precautions	Added additional background information in this section regarding flexible study conduct in response to COVID-19, including alternate collection methods for PROs (telephone or internet, not via mail)	Clarification per Health Authority request and to accurately reflect expected study conduct
CCI [redacted]		Correction

Table 28: Summary of Changes for Amendment 03 (Continued)

Section(s) Affected	Description of Change	Brief Rationale
CCI [redacted]		
Section 9.4.4. Secondary Analyses	Amended text in this section to specify descriptive-only analyses for DOR endpoint	Correction
Appendix 1. Guidelines for Assessment of Disease, Disease Progression, and Response Criteria (RECIST v1.1)	Clarified that, for stable disease assignment of best overall response, the follow-up disease assessment must have met stable disease criteria at least once after randomization at a minimum interval of 42 (±7), not 35 (±7) days.	For consistency with study scan schedule of every 6 weeks (42 days)
Appendix 7. Liver Safety Required Actions and Follow-Up Assessments/Table 23: Required Actions and Follow-up Assessments Following Any Liver Stopping Event	Clarified that acetaminophen adduct assay to assess liver injury should be conducted where available	Per the Sponsor's updated clinical study guidance
Appendix 12. Protocol Amendment History	Appendix 12 was updated to include the previous amendment (02) summary of changes information	Editorial changes to align with the Sponsor's standard protocol template and ways of working

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ALK=anaplastic lymphoma kinase; ctDNA=circulating tumor DNA; EGFR=epidermal growth factor receptor; IA=interim analysis;COVID-19=Coronavirus Disease 2019; DOR=duration of response; eCRF=electronic case report form; IDMC=independent data monitoring committee; IO=immuno-oncology; ORR=objective response rate; OS=overall survival; PD-L1=programmed death-ligand 1; PRO=patient-reported outcome; ROS-1=c-ros oncogene 1; SDAC=Statistical Data Analysis Center; TIM-3=T-cell immunoglobulin and mucin-domain containing-3; TPS=tumor proportion score.

Amendment 02 (21 October 2020)

Overall Rationale for Amendment 02

Amendment 02 was a global protocol amendment created in response to Health Authority feedback to provide a summary of safety data from Part 1f of the Sponsor's Study 4020-01-001 (AMBER; GSK Study 213348) in which the triplet combination of cobolimab + dostarlimab + docetaxel has been evaluated. A description and rationale for all changes is provided in Table 29.

Summary of Changes for Amendment 02

Table 29: Summary of Changes for Amendment 02

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; Protocol Amendment Summary of Changes section was updated	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Section 1.1. Synopsis (Treatment Groups and Duration) Table 1. Schedule of Activities Section 4.1. Overall Design Section 6.1.3. Docetaxel	Clarified that docetaxel infusion discontinuation is based on local label, toxicity, and disease progression	Consistent with label recommendations for discontinuation of docetaxel
Section 2.2.4. Rationale for Studying IO Therapy Combinations and IO Therapies in Combination with Chemotherapy in NSCLC	Added a summary of the safety data from Part 1f (triplet combination) of the AMBER study	Safety information from the Sponsor's cobolimab Investigator's Brochure (version 5, dated 31 July 2020) added to the protocol to support the study of cobolimab in combination with dostarlimab and docetaxel, per request of Health Authority

Section(s) Affected	Description of Change	Brief Rationale
Appendix 12. Protocol Amendment History	Creation of Protocol Amendment History appendix triggered to capture list of prior amendments now that there are multiple amendments to the original document. Information for Amendment 01 moved to Appendix 12 and replaced with Amendment 02 (current global amendment) information.	Editorial changes to align with the Sponsor's standard protocol template and ways of working

Abbreviations: IO=immuno-oncology; NSCLC=non-small cell lung cancer.

Amendment 01 (16 October 2020)

Overall Rationale for Amendment 01

Amendment 01 was a global protocol amendment created in response to Health Authority feedback to clarify that strong cytochrome P450 3A4 enzyme (CYP3A4) inhibitors are prohibited concomitant medications per the docetaxel label. Additionally, clarification was made that Coronavirus Disease 2019 (COVID-19) specifically may impact a participant's ability to attend site visits. A description and rationale for all changes is provided in Table 30.

Summary of Changes for Amendment 01

Table 30: Summary of Changes for Amendment 01

Section(s) Affected	Description of Change	Brief Rationale
Headers, cover page, and Protocol Amendment Summary of Changes	Headers and cover page were updated with new version number; Protocol Amendment Summary of Changes section was added per the Sponsor's protocol template as this is the first amendment for the protocol	Editorial changes to align with the Sponsor's standard protocol template and ways of working
Section 6.9.1 Prohibited Concomitant Medications and Nondrug Therapies	Added strong CYP3A4 inhibitors to the list of prohibited concomitant medications	Guidance added to avoid the use of strong CYP3A4 inhibitors when a participant is receiving docetaxel, to align with docetaxel prescribing guidelines, per request of Health Authority
Section 8.1.1. General Guidance for Treatment Continuity when Participants are Unable to Come into the Clinic	Added text that options presented in this section also apply to participants unable to travel to the clinic due specifically to restrictions from the COVID-19 pandemic.	To improve protocol clarity

Abbreviations: COVID-19=Coronavirus Disease 2019; CYP3A4=cytochrome P450 3A4 enzyme.

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