Statistical Analysis Plan

Study ID: 213406

Study Official Title: A Phase 1, Multicentre, Open-Label, Dose-Escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients With Recurrent or Refractory Solid Tumours

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TITLE PAGE

Protocol Title: A Phase 1, Multicentre, Open-label, Dose-escalation and Cohort Expansion Study of Niraparib and Dostarlimab in Paediatric Patients with Recurrent or Refractory Solid Tumours

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PPD Development Biostatistics

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study 213406 is based on the protocol v5.0dated 12 Dec 2024.

Table 1 SAP Version History Summary

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
SAP	06 Aug 2020	v1.1 (12-MAY-2020)	Not Applicable	Original version
SAP amendment 1	06 Jun 2025	V5.0 (12-DEC-2024)	Overall Study Design. CCI [redacted]	The overall study design is described in the master protocol. Originally under Protocol Amendment 03 (or earlier), the recommended Phase 2 dose (RP2D) for the combination of niraparib tablets and dostarlimab was determined in Part 1A of the study, which was opened to accrual for participants who were able to swallow the CCI [redacted] CCI and who had a body weight

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				of ≥20 kg. All participants were eligible to receive the RP2D of niraparib tablet and dostarlimab [redacted] mg). Under Protocol Amendment 03, [redacted] observed in Part 1B and Part 2 participants, and the original Part 1B portion of the study did not advance past Cohort 1. Following review and analysis of clinical, safety, and PK data for all study participants, a modified [redacted] was established for participants <8 years in Part 1B and a [redacted] was established for participants ≥8 years to <18 years in Part 2. This modification is included in Protocol Amendment 04. Under Protocol Amendment 04, Part 2 of this study will open to accrual for participants ≥8 years of age. All participants will receive the appropriate [redacted] and [redacted] Following the determination of the [redacted] RP2D for the combination of [redacted] in Part 1B of the study, Part 2 Cohort Expansion will be opened to enrolment of participants <8 years of age. These participants will be eligible to receive the RP2D of [redacted] as determined in Part 1B and [redacted]. Study treatment may continue until

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
				progressive disease (PD), unacceptable toxicity, participant withdrawal, Investigator's decision, or death. The Part 2 study design is illustrated in Figure 1. Under Protocol Amendment 04, enrolment in Part 2 will start with a Safety Run-in Cohort to confirm the safety, tolerability, and preliminary efficacy of the CCI [redacted] in participants with osteosarcoma and neuroblastoma.

1. INTRODUCTION

The purpose of this SAP is to describe the planned analyses to be included in the Clinical Study Report for Study 213406. Details of the planned interim analysis, as well as the final analyses, are provided.

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

1.1. Objectives, Estimands and Endpoints

1.1.1. Objectives and Endpoints

The objectives and endpoints for Part 1 of this study (Protocol 213406_Master) are detailed in the table below. The study design and endpoints for Part 2 of this study are detailed in the separate cohort-specific protocol supplements; however, the common objectives are summarized below.

Objectives	**Endpoints**
Primary	
Part 1A: Establish the RP2D of the combination of niraparib tablet and dostarlimab in paediatric participants	Assess the incidence of DLTs by study part and cohort for the DLT-evaluable population.
Part 1B: Establish the RP2D of the combination of CCI [redacted] CCI [redacted] in paediatric participants	Assess the incidence of DLTs by study part and cohort for the DLT-evaluable population.
Part 2: Assess the safety, tolerability, and the antitumour activity of the combination of niraparib and dostarlimab	Please refer to the separate cohort-specific supplements for this information.
Secondary	
Evaluation of measures of anticancer activity in paediatric participants	• ORR based on Investigator assessment is defined as the proportion of participants with a BOR of confirmed CR or PR as determined by the Investigator using RECIST v1.1 or INRC (for participants with neuroblastoma only). • DOR is defined as the time from first documentation of response confirmed (CR or PR) until the time of first

Objectives	Endpoints
	documented PD by RECIST v1.1 or INRC (for participants with neuroblastoma only) based on Investigator assessment or death (whichever occurs first). *Part 2: Please refer to the separate cohort-specific supplements for this information.*
Evaluation of the safety and tolerability of the combination of CCI [redacted] CCI [redacted] in paediatric participants	• Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
Characterisation of the PK of the combination of niraparib and dostarlimab in paediatric participants	• Niraparib and dostarlimab concentrations; PK parameters of niraparib and dostarlimab , if appropriate.
Assessment of the immunogenicity of dostarlimab in paediatric participants	• Rate and extent of ADA to dostarlimab.
CCI [redacted]	
Exploratory	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Abbreviations: ADA=antidrug antibody; AE=adverse event; BOR=best overall response; CR=complete response; DLT=dose-limiting toxicity; DOR=duration of response; INRC=International Neuroblastoma Response Criteria; imAE=immune-mediated adverse event; ORR=objective response rate; PD=progressive disease; PK=pharmacokinetic(s); PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose; SAE=serious adverse event; SOA=schedule of activities; TEAE=treatment-emergent adverse event; CCI [redacted] .

The following are the cohort-specific objectives for Part 2 Safety Run-In (Protocol 213406 Supplement A and Supplement B).

Objectives	Endpoints
Primary	
To assess the safety and tolerability of the CCI [redacted] by assessing DLT and Grade ≥3 thrombocytopenia AEs in paediatric participants	• Assess the incidence of DLTs in the Part 2 Safety Run-in for the DLT-evaluable Population. • Assess the incidence of Grade ≥3 thrombocytopenia AEs in the Part 2 Safety Run-in for the DLT-evaluable Population.
Secondary	
To evaluate measures of anticancer activity, including ORR, DOR, DCR, and PFS in paediatric participants	• ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma. • DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment or death (whichever occurs first). • DCR is defined as the proportion of participants who have achieved a

Objectives	Endpoints
	BOR of confirmed CR, confirmed PR, or stable disease by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment. • PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment, or death from any cause (whichever occurs first).
To evaluate the safety of the combination of CCI [redacted] in paediatric participants	• Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
To characterise the PK of niraparib in paediatric participants	• Niraparib concentrations; PK parameters of niraparib, if appropriate.

The following are the cohort-specific objectives for Part 2 Osteosarcoma Expansion Cohort (Protocol 213406_Supplement A).

Objectives	Endpoints
Primary	
Assessment of the antitumour activity of the combination of CCI [redacted], assessed primarily by PFS6 (using RECIST v1.1 criteria) in paediatric participants	• PFS6 is defined as the proportion of participants without PD per RECIST v1.1 criteria or death at 6 months from the date of the first dose of study treatment.
Secondary	
Evaluation of additional measures of anticancer activity including ORR, DOR, DCR, and PFS in paediatric participants	• ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using RECIST v1.1.
	• DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 based on Investigator assessment or death (whichever occurs first).
	• DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by RECIST v1.1 based on Investigator assessment.
	• PFS is defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by RECIST v1.1 based on Investigator assessment, or death from any cause (whichever occurs first).

Objectives	Endpoints
Evaluation of the safety of the combination of CCI [redacted] CCI [redacted] in paediatric participants	• Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
Characterisation of the PK of the combination of niraparib and dostarlimab in paediatric participants	• Niraparib and dostarlimab concentrations; PK parameters of niraparib and dostarlimab, if appropriate.
Assessment of the immunogenicity of dostarlimab in paediatric participants	• Rate and extent of anti-drug antibodies (ADA) to dostarlimab.
CCI [redacted]	
Exploratory	
CCI [redacted]	

Abbreviations: ; AE=adverse event; BOR=best overall response; CR=complete response; DCR=disease control rate, DOR=duration of response; imAE=immune-mediated adverse event; ORR=objective response rate; CCI [redacted]; PD=progressive disease; PD-1=programmed cell death protein 1; PFS=progression-free survival; PFS6=progression-free survival rate at 6 months; PK=pharmacokinetic(s); PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SAE=serious adverse event; SOA=schedule of activities; TEAE=treatment-emergent adverse event; CCI [redacted] CCI [redacted]

The following are the cohort-specific objectives for Part 2 Neuroblastoma Expansion Cohort (Protocol 213406_Supplement B).

Objectives	Endpoints
Primary	
Assess the antitumour activity of the combination of CCI [redacted], assessed primarily by ORR (using INRC) in paediatric participants	• ORR is defined as the proportion of participants who have a BOR of confirmed CR or PR as determined by the Investigator using INRC.
Secondary	
Evaluation of additional measures of anticancer activity including DOR, DCR, and PFS in paediatric participants	• DOR is defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC based on Investigator assessment or death (whichever occurs first). • DCR is defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC based on Investigator assessment. • PFS is defined as the time from the date of the first dose of study treatment to the first documented PD as determined by INRC based on Investigator assessment, or death from any cause (whichever occurs first).
Evaluation of the safety of the combination of CCI [redacted]) CCI [redacted] in paediatric participants	• Assess the incidence of TEAEs, SAEs, imAEs, TEAEs leading to death, and AEs leading to treatment discontinuation. AE evaluation period is while participants are on treatment or up to 90 days after the last dose of study treatment.
Characterisation of the PK of the combination of niraparib and dostarlimab in paediatric participants	• Niraparib and dostarlimab concentrations; PK parameters of niraparib and dostarlimab, if appropriate.

Objectives	Endpoints
Assess the immunogenicity of dostarlimab in pediatric participants	• Rate and extent of anti-drug antibodies (ADA) to dostarlimab
CCI [redacted]	
Exploratory	
CCI [redacted]	

Abbreviations: ; ADA=antidrug antibody; AE=adverse event; BOR=best overall response; CR=complete response; DCR=disease control rate, DOR=duration of response; INRC=International Neuroblastoma Response Criteria; imAE=immune-mediated adverse event; ORR=objective response rate; CCI [redacted]; PD=progressive disease; PD-1=programmed cell death protein 1; PFS=progression-free survival; PK=pharmacokinetic(s); PR=partial response; SAE=serious adverse event; SOA=schedule of activities; TEAE=treatment-emergent adverse event; CCI [redacted]

1.1.2. Estimands

Study 213406 is a Phase 1 dose-finding safety study with a primary objective of establishing the RP2Ds in the master protocol (dose escalation cohorts of Part 1A and Part 1B) and assessment of safety and tolerability in Part 2 Safety Run-In. Antitumour/Anticancer activity assessment are included as a secondary objective in the master protocol and Part 2 Safety Run-In, and primary/secondary objective in the supplement protocols (dose expansion cohorts), respectively. The corresponding efficacy endpoints are listed below:

- ORR
  - The primary objective in Part 2B Expansion
  - A secondary objective in Part 1A, Part 1B, Part 2 Safety Run-In and Part 2A Expansion
- PFS6 (binary endpoint)
  - The primary objective in Part 2A Expansion

- DOR
  - A secondary objective in Part 1A, Part 1B, Part 2 Safety Run-In, Part 2A Expansion, and Part 2B Expansion
- DCR and PFS
  - A secondary objective in Part 2 Safety Run-In, Part 2A Expansion) and Part 2B Expansion

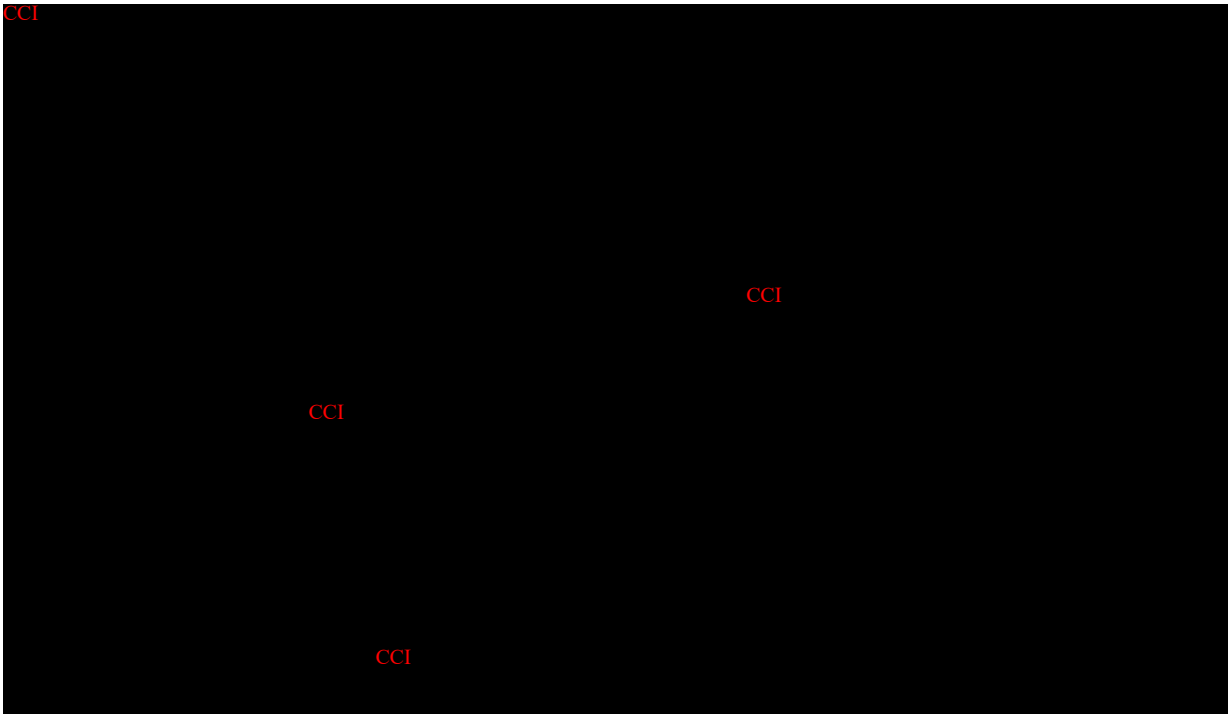
The primary Estimands for the efficacy endpoints aforementioned are summarized in Table 2.

Table 2 Estimands

Estimand Category	Estimand			
	Variable/ Endpoint	Analysis Set	Intercurrent Event Strategy	Population Level Summary Measure
Primary	ORR	ITT (Part 1A/1B) mITT (Safety Run-In, Part 2A/2B)	• New anti-cancer therapy: hypothetical • Treatment discontinuation: treatment policy	Descriptive summary by cohorts
Primary	DCR	mITT (Safety Run-In, Part 2A/2B)		
Primary	PFS6	mITT (Part 2B)	• New anti-cancer therapy: treatment policy • Treatment discontinuation: treatment policy • Death: composite	Descriptive summary
Primary	DOR	ITT (Part 1A/1B) mITT (Safety Run-In, Part 2A/2B)	• New anti-cancer therapy: hypothetical • Treatment discontinuation: treatment policy • ≥2 consecutive missing tumour assessments: hypothetical • Death: composite	Summarized using the Kaplan-Meier method by cohorts
Primary	PFS	mITT (Safety Run-In, Part 2A/2B)		

Abbreviations: ORR=objective response rate; DCR=disease control rate; DOR=duration of response; PFS=progression-free survival; PFS6= progression-free survival rate at 6 months; ITT= Intent-to-treat; mITT= Modified Intent-to-Treat.

1.2. Study Design



Overview of Study Design and Key Features
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Overview of Study Design and Key Features

a. The study will not continue as designed. Alternate niraparib schedules (such as dosing during 2 of 3 weeks) and/or conversion to body surface area-based dosing may also be implemented for niraparib, if appropriate.

Following the enrolment pause and review and analysis of clinical, safety and PK data for all study participants, Part 1B restarted using a modified CCI [redacted] The starting dose level for dostarlimab (DL1) will be the RP2D as determined from Part 1A (CCI [redacted]

The planned dose escalation schema for the reopened Part 1B is below. PK evaluations will be performed in at least 6 participants in each cohort unless enrolment into the cohort is closed prematurely due to toxicity.

CCI [redacted]

Design Features	• This is a Phase 1, multicentre, open-label, dose-escalation study (Part 1) with Safety Run-in and a Cohort Expansion component (Part 2). The study will consist of an initial dose-escalation portion conducted in participants CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] Part 1A: a dose escalation to determine the RP2D of the combination of CCI [redacted] CCI [redacted] will include participants who are able to swallow the CCI [redacted] and who have a body weight of ≥20 kg.

Overview of Study Design and Key Features	
	• Part 1B: a dose escalation to determine the RP2D of the combination of CCI [redacted] under Protocol Amendment 03 (or earlier), included participants who cannot swallow the CCI [redacted] or who had a body weight of <20 kg. Part 1B under Protocol Amendment 04 and later, will include participants who are <8 years of age and will receive a modified CCI [redacted] • Part 2: the RP2D regimen established in Part 1 of the study will be evaluated for efficacy and safety in disease specific expansion cohorts and Safety Run-In: to confirm the safety, tolerability, and preliminary efficacy of the CCI [redacted] CCI [redacted] in participants with osteosarcoma and neuroblastoma, will include participants who are ≥8 years old o Safety Run-In: Osteosarcoma and Neuroblastoma o Part 2A: Osteosarcoma Expansion Cohort o Part 2B: Neuroblastoma Expansion Cohort
Study intervention	CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]. Dostarlimab infusion will be administered before the niraparib dose at the study site on Day 1 of each 21-day treatment cycle (Q3W). Dostarlimab will be administered through a 30-minute infusion. A window between -5 minutes and +15 minutes is permitted, in the absence of any clinically significant infusion-related reaction that would necessitate interruption and/or increased infusion interval.
Study intervention Assignment	Under Protocol Amendment 03, approximately 56 participants were planed to be dosed with the combination of CCI [redacted] at pre-specified dose escalation dose levels in Part 1 including approximately 32 participants in Part 1A and approximately 24 participants in Part 1B (unless the incidence of DLTs dictated fewer participants as per the Dose Escalation Plan described). A total of 23 participants were enrolled into Part 1A Cohorts 0, 1A, and 1B. Part 1A Cohort 1B was not deemed to be safe, and, as a result, no participants were enrolled into

Overview of Study Design and Key Features	
	Part 1A Cohort 2. In addition, a total of 3 participants were enrolled into Part 1B Cohort 1, for which enrolment into Part 1B Cohort 1 was prematurely stopped due to DLTs of Grade ≥3 thrombocytopenia. Under Protocol Amendment 04 and after, it is anticipated that, 1 to 3 cohorts (up to 8 participants per cohort or approximately 24 participants overall) may be enrolled in Part 1B, unless the incidence of DLTs dictates fewer participants as noted in Section 4.1. Additional cohorts (including up to 8 participants per cohort) may be opened in Part 1B if needed to evaluate alternative niraparib dose levels. Lastly, up to 5 additional participants may be enrolled into Part 1B to further evaluate the youngest participant group(s) if not represented Approximately 60 participants may be dosed with the combination of CCI [redacted] at RP2D level in Part 2 (including eligible participants with osteosarcoma and neuroblastoma from the Safety Run-in).
Interim Analysis	For Part 1 of the study, in accordance with the Sponsor's standard operating procedure, the DEC will monitor intervention-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of participants enrolled in this study as described in detail in the Dose Escalation Plan. Once all participants in the Safety Run-in have been observed for ≥42 days, all available data from the Part 2 Safety Run-in together with all data previously collected under Protocol Amendment 03 and earlier will be reviewed with the study DEC and the Data Review Committee (DRC) before additional participants on Part 2 are enrolled. CCI [redacted]

2. STATISTICAL HYPOTHESES / SUCCESS CRITERIA

Part 1 and Part 2 Safety Run-In: Not applicable

Part 2A

- $H_0: PFS6 \leq 10\%, \quad H_1: PFS6 \geq 30\%$
- Simon's 2-stage optimal design with a 1-sided alpha of 0.05
  - Stage 1 (10 participants) success criterion: at least 2 out of 10 participants remain progression free after 6 months
  - Stage 2 (29 participants) success criterion: after enrolling additional 19 participants, 6 or more out of 29 participants remain progression free after 6 months

Part 2B

- $H_0: ORR \leq 10\%, \quad H_1: ORR \geq 30\%$
- Simon's 2-stage optimal design with a 1-sided alpha of 0.05
  - Stage 1 (10 participants) success criterion: at least 2 out of 10 participants have confirmed objective responses (CR or PR)
  - Stage 2 (29 participants) success criterion: after enrolling additional 19 participants, 6 or more out of 29 participants have confirmed objective responses (CR or PR)

2.1. Multiple Comparisons and Multiplicity

Not applicable

3. ANALYSIS SETS

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• The Screened Population will consist of all participants who sign the ICF to participate in the clinical trial. Participants in this population will be used for screen failure summary.	• Study Population
Safety	• The safety population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.	• Study population • Safety
Intent-to-Treat (ITT)	• The intent-to-treat population includes all participants who receive any study medication and have measurable baseline tumour assessment and/or, for neuroblastoma participants, metaiodobenzylguanidine-positive disease (MIBG) (or FDG-positive disease, for MIBG-nonavid tumours) at baseline.	• Efficacy
Modified Intent-to-Treat (mITT)	• The mITT population includes all participants who receive any study medication, have measurable baseline tumour assessment, and/or, for neuroblastoma participants, MIBG-positive disease (or FDG-PET positive disease, for MIBG-nonavid tumours)and have at least 1 post baseline tumour assessment.	• Efficacy
Per-Protocol	• The per-protocol population includes all participants in the mITT population who do not have protocol violations during the study that may significantly impact the interpretation of efficacy results.	• Efficacy
DLT-Evaluable	• The DLT-evaluable population consists of participants in Part 1 who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2	• DLT

Analysis Set	Definition / Criteria	Analyses Evaluated
	infusions of dostarlimab) or experience a DLT. • The DLT-evaluable Population consists of participants in Part 2 Safety Run-in who complete the DLT observation period through at least 2 cycles of study treatment (including ≥80% of the intended niraparib dose and ≥2 infusions of dostarlimab) or experience a DLT for DLT endpoint (or Grade ≥3 thrombocytopenia AEs for the thrombocytopenia event endpoint).	
Pharmacokinetic (PK)	• The PK population includes all participants who receive at least one dose of study treatment and have at least one PK sample. PK populations are defined separately for each agent.	• PK
Immunogenicity (ADA) Population	• All participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with result.	• ADA Population

3.1. Definitions for Per Protocol Analysis Set

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, participant management or participant assessment) will be summarized and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study. These protocol deviations will be reviewed to identify those considered as important as follows:

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

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

The safety analysis set will be used for both study population and safety analysis. The DLT-evaluable analysis set will be used for DLT and Thrombocytopenia Grade ≥3 AEs analysis. The Intent-to-Treat (ITT) analysis set will be used for efficacy analyses in Part 1. The Modified Intent-to-Treat (mITT) analysis set will be used for efficacy analyses in Part 2. Per-protocol analysis set maybe used for sensitivity efficacy analysis in Part 2.

Confidence intervals will use two-sided 95% confidence levels unless otherwise specified.

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum and maximum. Categorical data will be summarized as the number and percentage of participants in each category.

Missing data will not be imputed unless otherwise stated.

4.1.2. Baseline Definition

For all endpoints the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

4.1.3. Multicenter Studies

Data from all participating centers will be integrated and no controlling for center-effect will be considered in the statistical analyses. It is anticipated that participant accrual will be spread thinly across centers and summaries of data by center is unlikely to be informative and will not be provided.

4.2. Primary Endpoint(s)/Estimand(s) Analyses

4.2.1. Definition of endpoint(s)

Part 1: Dose-limiting toxicity (DLT) and Part 2 Safety Run-In

DLT is the primary endpoint in Part 1 and Part 2 Safety Run-In. Thrombocytopenia events is a co-primary endpoint in Part 2 Safety Run-In. The incidence of DLTs and thrombocytopenia events will be summarised by study part and cohort for the DLT-evaluable analysis set.

DLT is defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related Grade 4 nonhaematologic clinical (nonlaboratory) AE
- any treatment-related Grade 3 nonhaematologic clinical (nonlaboratory) AE not resolving to Grade ≤1 within 48 hours of initiating optimal medical intervention
- any treatment-related Grade 3 or 4 nonhaematologic laboratory abnormality if any of the following also occur:
  - the abnormality leads to hospitalization
  - the abnormality persists for ≥7 days from the time of AE onset and participant is symptomatic from the AE and/or requires intervention
- any treatment-related haematologic toxicity defined as any of the following:
  - Grade 4 thrombocytopenia persists for ≥7 days from the time of AE onset or Grade 3 or 4 thrombocytopenia associated with clinically significant bleeding or requiring platelet transfusion
  - Grade 4 neutropenia persists for ≥7 days, Grade 3 or 4 neutropenia associated with infection, or Grade 3 or 4 febrile neutropenia persists for ≥72 hours
  - Grade 4 anaemia or Grade 3 anaemia requiring blood transfusion
- any treatment-related toxicity leading to prolonged delay (>2 weeks) in initiating Cycle 2
- any treatment-related Grade ≥2 uveitis, eye pain, or blurred vision that does not resolve with topical therapy within 2 weeks
- any treatment-related Grade ≥2 immune-related endocrine toxicity that requires hormone replacement, except Grade 2 thyroiditis or thyroid dysfunction
- any treatment-related Grade 2 colitis or diarrhoea that persists for ≥7 days without resolution to Grade ≤1 despite adequate steroid therapy
- any Grade 3 or 4 immune-mediated adverse event (imAE) that does not resolve to Grade ≤1 or baseline within 8 days despite adequate immune suppressive therapy
- Grade 3 or higher infusion-related reaction.
- any grade of hemophagocytic lymphohistiocytosis
- any treatment-related Grade 5 AE
- any grade of Posterior Reversible Encephalopathy Syndrome (PRES)
- The following criterion is part of the DLT criteria for Part 1 only. It is not a part of the DLT criteria for Part 2 Safety Run-In: any treatment-related toxicity resulting in the participant receiving <80% of the intended niraparib dose and/or <2 dostarlimab infusions due to dose modification/interruption/ reduction.

Thrombocytopenia events for Part 2 are defined as any of the following occurring during the first 42 days of study treatment:

- any treatment-related toxicity defined as any of the following:
    - Grade 3 or Grade 4 thrombocytopenia

Part 2A: PFS6

The primary efficacy endpoint for Part 2A is PFS6, defined as the proportion of participant without PD per RECIST v1.1 criteria or death at 6 months from the date of the first dose of study treatment. Analysis will be conducted after participants have been followed up for at least 6 months, have documented progression, withdrawn from the study or have died.

Part 2B: ORR

The primary efficacy endpoint for Part 2B is ORR based on Investigator assessment, defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using INRC. Analysis will be conducted after participants have been followed up for at least 6 months (i.e. at least 3 post baseline scans (i.e. approximately 6.2 months), have documented progression, withdrawn from the study or have died.Main analytical approach

Part 1 and Part 2 Safety Run-In: DLT

The incidence of DLT will be estimated as the proportion of participants with DLTs at each dose level from Part 1A, Part 1B and Part 2 Safety Run-In respectively. The analysis will be performed on the DLT-evaluable analysis set.

Part 2 Safety Run-In

The incidence of thrombocytopenia events will be estimated as the proportion of participants with thrombocytopenia events in the Safety Run-In. The analysis will be performed on the DLT-evaluable analysis set.

Part 2A: PFS6

PFS6 will be estimated as the proportion of participant without PD per RECIST v1.1 criteria or death at 6 months from the date of the first dose of study treatment. PFS6 is evaluated as a binary endpoint. The two-sided 95% exact (Clopper-Pearson) confidence interval will also be provided. For consistency with the design, the lower bound of one-sided 95% exact (Clopper-Pearson) confidence interval will also be provided. The analysis will be performed on the mITT analysis set.

Part 2B: ORR

ORR will be estimated as the proportion of participant with confirmed CR or PR as determined by the Investigator using INRC. The two-sided 95% exact (Clopper-Pearson) confidence interval will also be provided. For consistency with the design, the lower bound of one-sided 95% exact (Clopper-Pearson) confidence interval will also be provided. The analysis will be performed on the mITT analysis set.

4.2.2. Sensitivity analyses

Part 1: Not applicable

Part 2A: PFS6 will also be estimated using non-parametric Kaplan-Meier method on the mITT analysis set. The two-sided 95% confidence interval using the log-log transformation will be provided (Brookmeyer-Crowley method).

- ITT and Per-protocol analysis set may also be used to estimate PFS6

Part 2B: ORR

- ITT and Per-protocol analysis set may also be used to estimate ORR

4.3. Secondary Endpoint(s)/Estimand(s) Analyses

4.3.1. Secondary efficacy endpoint(s)

For Part 1 and Part 2 Safety Run-In secondary efficacy endpoints, the analysis will be based on ITT analysis set. For Part 2A and Part 2B secondary efficacy endpoints, the analysis will be based on mITT analysis set.

4.3.1.1. Definition of endpoint(s)

Part 1

- Overall response rate (ORR), defined as the proportion of participants with a best overall response (BOR) of confirmed CR or PR as determined by the Investigator using RECIST v1.1 or onfirmed CR or PR as determined by INRC (for participants with neuroblastoma only).
- Duration of response (DOR), defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 or INRC (for participants with neuroblastoma only) based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmed CR or PR. Participants who do not experience PD or die after they have had a response are censored at the date of their last tumour assessment. Detailed DOR censoring rules are provided in Table 3.

Part 2 Safety Run-In

- ORR, defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma.
- DOR, defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmed CR or PR. Participants

who do not experience PD or die after they have had a response are censored at the date of their last tumour assessment. Detailed DOR censoring rules are provided in Table 3

- Disease Control Rate (DCR), defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment.
- Progression-free Survival (PFS), defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC for participants with neuroblastoma or RECIST v1.1 for participants with osteosarcoma based on Investigator assessment, or death from any cause (whichever occurs first). Participants without an event will be censored at the date of the last tumour assessment. Participants without postbaseline assessments will be censored at the date of the first dose. Detailed PFS censoring rules are provided in Table 4

Part 2A

- ORR, defined as the proportion of participants who have a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) as determined by the Investigator using RECIST v1.1.
- DOR, defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by RECIST v1.1 based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmedCR or PR. Participants who do not experience PD or die after they have had a response are censored at the date of their last tumour assessment. Detailed DOR censoring rules are provided in Table 3
- Disease Control Rate (DCR), defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by RECIST v1.1 based on Investigator assessment.
- Progression-free Survival (PFS), defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by RECIST v1.1 based on Investigator assessment, or death from any cause (whichever occurs first). Participants without an event will be censored at the date of the last tumour assessment. Participants without postbaseline assessments will be censored at the date of the first dose. Detailed PFS censoring rules are provided in Table 4

Part 2B

- DOR, defined as the time from first documentation of confirmed response (CR or PR) until the time of first documented PD by INRC based on Investigator assessment or death (whichever occurs first). This will only be calculated for participants who have a BOR of confirmed CR or PR. Participants who do not experience PD or die after they have had a response are censored at the date of their last tumour assessment. Detailed DOR censoring rules are provided in Table 3

- DCR, defined as the proportion of participants who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC based on Investigator assessment (assessment of MR will be assigned SD for the purpose of DCR evaluation).
- PFS, defined as the time from the date of the first dose of study treatment to the first documented PD, as determined by INRC based on Investigator assessment, or death from any cause (whichever occurs first). Participants without an event will be censored at the date of the last tumour assessment. Participants without postbaseline assessments will be censored at the date of the first dose. Detailed PFS censoring rules are provided in Table 4

Table 3 Censoring rules used in DOR analysis

Situation	Date of Event or Censoring	Outcome
Start of subsequent anti-cancer therapy prior to a documented progression or death	Date of last evaluable radiological tumour assessment on or prior to the date of initiation of the subsequent anti-cancer therapy).	Censored
Free of progression or death and no subsequent anti-cancer therapy started	Date of last evaluable radiological tumour assessment	Censored
Documented progression or death after two or more consecutive missing radiological tumour assessments	Date of last evaluable tumour assessment prior to the consecutive missing assessments. A window of 133 days (18 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment following the start of study treatment for the first 12 months and then a window of 175 days (every 24 weeks [±7] days) thereafter. If the time difference between PD/death and last adequate disease assessment is more than 133 days following the start of study treatment for the first 12 months, and 175 days thereafter, DOR will be censored at the last adequate disease assessment prior to PD/death.	Censored
Documented progression prior to initiation of new anticancer treatment and two or more consecutive missing radiological tumour assessments or death	Earliest date of documented tumour progression or death	Event

Table 4 Censoring rules used in PFS analysis for the primary estimand

Situation	Date of Event or Censoring	Outcome
No evaluable baseline or post-baseline radiological tumour assessments[a], and no death	First dose date	Censored
No [b] post baseline assessment before the start of new anticancer therapy and the participant has not died.	First dose date	Censored
With adequate[b] post-baseline assessment and start of subsequent anti-cancer therapy prior to a documented progression or death[d]	Date of last evaluable/ adequate[b] radiological tumour assessment on or prior to the date of initiation of the subsequent anti-cancer therapy.	Censored
With adequate[b] post-baseline assessment and free of progression or death and no subsequent anti-cancer therapy started	Date of last evaluable/ adequate[b] radiological tumour assessment	Censored
Death (regardless of having baseline assessment) before missing 2 scheduled assessments and no progression	Event on date of death: a window of 133 days (18 weeks + 7-day window) will be used to determine whether there is extended time before death without adequate assessment following the start of study treatment for the first 12 months and then a window of 175 days (every 24 weeks [±7] days) thereafter.	Event
Documented progression or death (regardless of having baseline assessment) after two or more consecutive missing radiological tumour assessments	Censored at first dose date if there is no adequate post-baseline assessment or date of last evaluable/ adequate[b] radiological tumour assessment prior to the consecutive missing assessments. A window of 133 days (18 weeks + 7-day window) will be used to determine whether there is extended time without adequate assessment following the start of study treatment for the first 12 months and then a window of 175 days (24 weeks [±7] days) thereafter. If the time difference between PD/death and last adequate disease assessment is	Censored

Situation	Date of Event or Censoring	Outcome
	more than 133 days following the start of study treatment for the first 12 months, and 175 days thereafter, PFS will be censored at the last adequate disease assessment prior to PD/death.	
Documented progression between scheduled visits	Event on date of assessment of progression[c]	Event
Death before first scheduled assessment	Event on date of death	Event
Treatment discontinuation due to clinical progression before PD or death	Not Applicable	Not Applicable

a. Participants are considered as not having baseline assessments if there is no disease assessment within 28 days of enrollment.
b. An adequate assessment is defined as an assessment where the investigator/independent reviewer determined response is CR, PR, or SD.
c. The earliest of (i) Date of radiologic assessment showing new lesion (if progression is based on new lesion); or (ii) Date of radiologic assessment showing unequivocal progression in non-target lesions, or (iii) Date of last radiologic assessment of measured lesions (if progression is based on increase in sum of measured lesions).
d. If PD and subsequent anticancer therapy occur on the same day, assume the progression was documented first, e.g., outcome is progression and the date is the date of the assessment of progression.

4.3.1.2. Main analytical approach

ORR will be estimated as the proportion of participant who have a BoR with confirmed response for CR and PR as determined by the Investigator using RECIST v1.1 or confirmed CR or PR as determined by the Investigator using INRC (for participants with neuroblastoma only). The two-sided 95% exact (Clopper-Pearson) confidence interval will also be provided. The summary will be based on each dose cohort in Part 1, Part 2 Safety Run-In and Part 2A and 2B expansions. A listing will be provided if the number of participants in a cohort is small. DCR will be estimated as the proportion of participant who have a BoR with confirmed response (CR or PR), or stable disease (without subsequent cancer therapy) for at least 17 weeks (119 days) after start of treatment (to allow for an early assessment of 18 weeks within the ± 1-week assessment window) as determined by the Investigator (assessment of MR will be assigned SD for the purpose of DCR evaluation). The 95% exact (Clopper-Pearson) confidence interval will also be provided. The summary will be based on each dose cohort in Part 1, Part 2 Safety Run-In, and Part 2A and Part 2B expansions. A listing will be provided if the number of participants in a cohort is small.

DOR will be summarized using the Kaplan-Meier method. The median, 25th and 75th percentiles of DOR will be estimated and corresponding two-sided 95% confidence intervals will be estimated using the log-log transformation (Brookmeyer-Crowley method). The summary will be based on each dose cohort in Part 1, Part 2 Safety Run-In, and Part 2A and Part 2B expansions. A listing will be provided if the number of participants in a cohort is small.

PFS will be summarized using the Kaplan-Meier method. The median, 25th and 75th percentiles of PFS will be estimated and corresponding two-sided 95% confidence intervals will be estimated using the log-log transformation (Brookmeyer-Crowley method). The summary will be based on Part 2 Safety Run In, and Part 2A and Part 2B expansions. A listing will be provided if the number of participants in a cohort is small.Best overall response (BOR) will be derived to calculate the efficacy endpoints. Best overall response is defined as the best response recorded from first dose until the criteria for progression are met, the initiation of new anticancer therapy, or death, whichever is earliest. The order from best to worst of the available responses is CR, PR, , SD, PD and not evaluable (NE) (assessment of MR will be assigned SD for the purpose of BOR evaluation). The number and percentage of participants for each available BOR will be provided with confirmation for RECIST v1.1 and INRC. For the derivation with (consecutive) confirmation for RECIST v1.1 these additional points need to be considered:

- 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.
- Responses of CR/PR that do not meet the requirements of confirmed CR/PR are still eligible to be considered SD if it has met the SD criteria.
- Assessments that are not done or are not evaluable can be disregarded when checking for confirmation. For example, a participant with PR-NE-PR is a confirmed PR response.
- To be assigned a status of SD, follow-up disease assessment must have met the SD criteria at least once after first dose of study treatment at a minimum interval of 8 weeks (56 days) from baseline, that is first scheduled imaging interval (9 weeks) minus 1 week window. Note that duration of stable disease (SD for RECIST) is measured from the date of first dose until the last adequate non-PD response.

If the minimum duration for SD is not met, the best overall response will depend on the subsequent assessments. If an assessment of PD follows the assessment of SD and SD does not meet the minimum requirement, the best response will be PD. Alternatively, participants with no further adequate assessments, after an SD assessment not meeting the minimum time criteria, will be considered not evaluable. Confirmed best overall response per RECIST v1.1 and INRC will be derived according to Table 5.

Table 5 Best Overall Response per RECIST 1.1 and INRC

Overall Response First time point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[1]
CR	SD	SD provided minimum criteria for SD met[2], otherwise PD
CR	PD	SD provided minimum criteria for SD met[2], otherwise PD

Overall Response First time point	Overall Response Subsequent Time Point	Best Overall Response
CR	NE	SD provided minimum criteria for SD met[2], otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD provided minimum criteria for SD duration met[2]. otherwise NE
PR	PD	SD provided minimum criteria for SD duration met[2], otherwise PD
PR	NE	SD provided minimum criteria for SD duration met[2], otherwise NE
SD	SD	SD provided minimum criteria for SD duration met[2], otherwise NE
SD	PD	SD provided minimum criteria for SD duration met[2], otherwise PD
SD	NE	SD provided minimum criteria for SD duration met[2], otherwise NE
NE	NE	NE

[1] If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

[2] Minimum criteria for SD disease duration is at least 8 weeks (56 days) to qualify as SD for BOR.

Note: If Best Overall Response is CR or PR, the participant is classified as a responder for the ORR analysis.

4.3.1.3. Sensitivity analyses

Part 1 and Part 2 Safety Run-In: Not applicable

Part 2A and 2B Expansions: ITT and per-protocol analysis sets may be used for the secondary efficacy analyses.

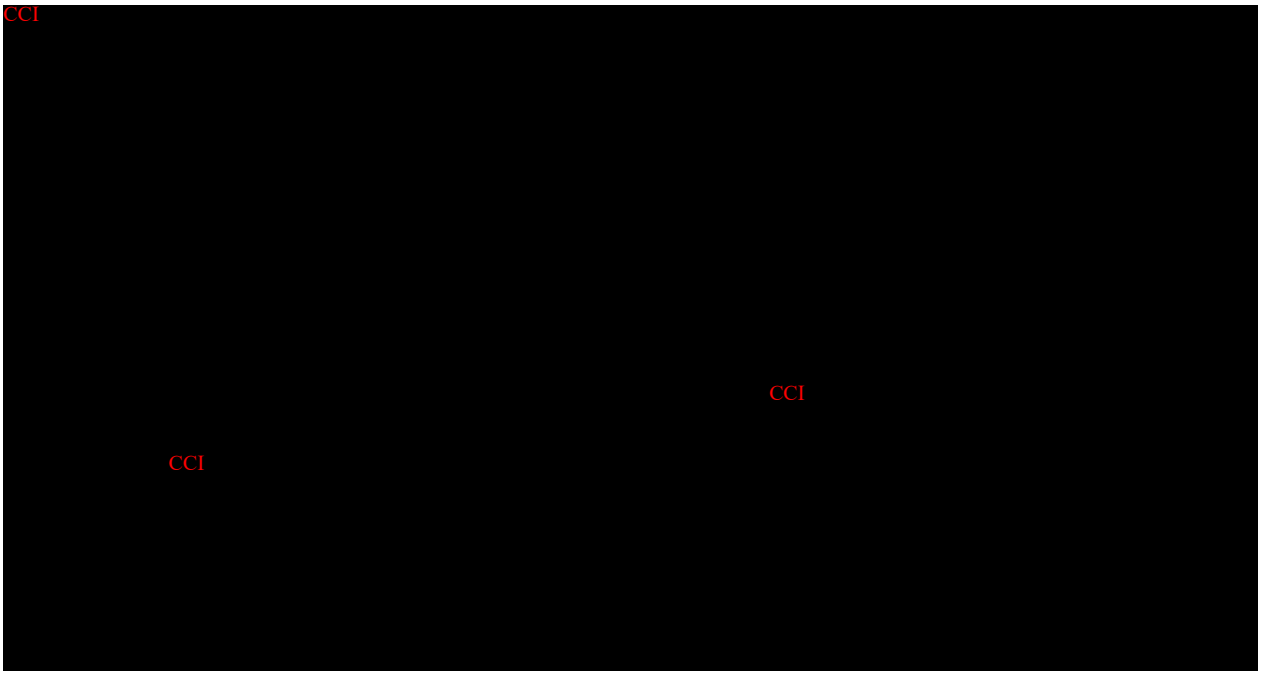
4.3.2. Other secondary endpoint(s)

4.3.2.1. Pharmacokinetic Analyses

The PK analyses will be based on the PK analysis set. The PK characteristics of niraparib and dostarlimab may be evaluated in the PK population of this study using sparse blood sampling and population PK approaches. Serum concentrations of dostarlimab and CCI [redacted] will be presented using descriptive statistics by dose cohort. Summary statistics will include mean, standard deviation, coefficient of variation (CV), geometric mean, geometric mean CV, median, and minimum and maximum values. The CCI [redacted] data may be used to evaluate the age-related development of niraparib metabolism in paediatric participants, if data permit. A nonlinear mixed effects model may be used to determine population pharmacokinetic parameters and identify relevant covariates (e.g., age,

weight, or disease-related covariates). The data from this study may be combined with data from other studies, which will be reported in a separate report.

In addition, if deemed appropriate and if data permit, exposure-response relationships between exposure (e.g., dose, dose intensity, concentration, maximum concentration, or area under the concentration-time curve) and clinical activity and/or toxicity (e.g., response, [exploratory] biomarkers, safety event) may be explored using population modelling approaches. If data permit, the effects of covariates may be explored. Results of such analysis will be reported in a separate report.



4.3.2.3. Immunogenicity (Anti-Drug Antibody) Analyses

Blood samples for the evaluation of dostarlimab ADAs and NAb with associated drug concentration will be obtained at the time points specified in as per Schedule of Activity. Serum samples for the determination of anti-dostarlimab antibodies will be aliquots of the same samples collected as for PK. ADAs will be analysed in a tiered approach (i.e., screening, confirmation, titre, and neutralising antibody assay) using electrochemiluminescence, if appropriate.

Immunogenicity will be analysed in the immunogenicity (ADA) Population. ADA are to be evaluated in all pre dose samples collected at each specified time point. The number and percent of participants in each ADA/nAb category will be summarised by visit/time and overall based on study part and cohort/regimen. Treatment emergent ADA will be evaluated for participants who receive at least 1 dose of study treatment and have at least samples have at least one available ADA result at pre-dose and following first dose. Additional TFLs may be generated to assess dostarlimab immunogenicity.

4.4. Tertiary/Exploratory Endpoint(s) Analyses

CCI [redacted]

4.5. (Other) Safety Analyses

The safety analyses will be based on the Safety Analysis Set, and by study part and cohort and overall, unless otherwise specified.

4.5.1. Extent of Exposure

4.5.1.1. Niraparib Exposure

Protocol amendment 3 and earlier: Overall treatment compliance during the DLT evaluation period for Niraparib is calculated based on the following (not based on age, not Part 1B):

- The number of doses taken is assessed based on the 'Exposure as Collected' data, only taking into account doses up to study day 42 as a maximum. The number of doses the participant received is based on the durations of exposure collected in this data up to day 42, as well as the frequency of the doses.
- Per the protocol, participants are expected to receive one dose per day, thus the calculation is based on an expected number of doses of 42 for the 42-day period.
- The calculation is as follows: (number of doses consumed within the first 42 days * treatment duration of participant in first 42 days)/ planned expected dose. For Part 1A Cohort 0 and Part 1A Cohort 1A the planned expected dose is 42* CCI where for Cohort 1B the planned expected dose is 42* CCI)*100.
- Participants need a Niraparib compliance during this period of 80% or higher to be considered for DLT-evaluability (in the absence of a DLT during this period).

Protocol amendment 4 and after: Overall treatment compliance during the DLT evaluation period for Niraparib Part 1B participants and Safety Run In who are less than 8 age years (Cohort A only) will be calculated CCI as shown below.

- Participants whose age is 0.5 years, are expected to receive an average dose of CCI mg/day in first 42 days, which is 21, the schedule is CCI Treatment compliance for this age group is calculated as follows: (number of doses consumed within the first 42 days / expected doses in first 42 days)* CCI For example: if participant had taken 20 doses of an average dose of CCI mg/day in 42 days and the planned dose is 21, compliance value for this participant will be CCI *100=95.2%

- Participants whose age is 1 year, are expected to receive an average dose as CCI mg/day in first 42 days, which is 30 days, the schedule is CCI Treatment compliance for this age group is calculated as follows: (number of doses consumed within the first 42 days / expected doses in first 42 days)*100. For example: if participant had taken 20 doses in 42 days the planned dose will be 30 doses, compliance value for this participant will be (20/30) *100=66.6%.
- Participants whose age is 2 years, are expected to receive an average dose as CCI mg/day in first 42 days, which is 30 doses, the schedule is CCI CCI The calculation is as follows: (number of doses consumed within the first 42 days / expected doses in first 42 days) *100. For example: if participant has taken 20 doses in 42 days the planned dose will be 30 doses. So, compliance value for this participant will be (20/30) *100=66.6%
- Participants whose age 3 or older and who are younger than 8, are expected to receive an average dose as CCI CCI in first 42 day. The calculation is as follows: (number of doses consumed within the first 42 days/ planned expected dose within the first 42 days)*100.

Overall treatment compliance during the DLT evaluation period for Niraparib Part 2 participants who are 8 years and less than 18 will be calculated CCI in kg. The calculation is as follows: (number of doses consumed within the first 42 days/ planned expected dose within the first 42 days)*100.

CCI or CCI

Treatment exposure will be summarized as follows:

- Number of cycles started summarized as a continuous variable.
- Overall treatment exposure (months), defined as the [(last dose date, data cutoff date) - first dose date + 1] / 30.4375, will be summarize as a continuous variable.
- Actual treatment exposure (months), defined as the overall treatment exposure minus the duration of dose interruptions, will be summarized as a continuous variable.
- Time on study (months), defined as the [(last contact date, date of death, data cutoff date) - first dose date + 1] / 30.4375, will be summarized as a continuous and categorical variables.

Treatment compliance will be summarized using study treatment data up to the last dose date by data cut-off date as follows:

- Cumulative dose is calculated as actual treatment exposure in days multiplied by actual dose taken (mg) at each time point of treatment administration.
- Dose intensity (mg/day), defined as cumulative dose divided by overall treatment exposure (converted to days), will be summarized as a continuous variable.
- Relative dose intensity (RDI, %), defined as dose intensity (mg/day) divided by intended dose intensity (mg/day) multiplied by 100, where intended dose intensity is the intended starting dose, will be summarized as a continuous variable.

- Dose intensity, dose reductions and dose interruptions will be summarized:
    - Number and percentage of participants with a dose reduction, as indicated on the dose modification eCRF, for any reason and due to an AE. The reasons for reduction will be summarized with number and percentage for each reason. Number and percentage of participants with a dose reduction by cycle will be summarized.
    - Number and percentage of participants with a dose interruption, as indicated on the dose modification eCRF, for any reason and due to an AE. The reasons for interruptions will be summarized with number and percentage for each reason. Number and percentage of participants with a dose interruption by cycle will be summarized.

Dosing information and tablets or CCI for each participant will be presented in a data listing.

4.5.1.2. Dostarlimab Exposure

Treatment compliance during the DLT evaluation period for Dostarlimab is calculated based on the following:

- The number of infusions administered is assessed based on the 'Exposure as Collected' data, only taking into account infusions up to study day 42 as a maximum. The number of infusions is calculated as the number of records (with a study day of less than or equal to 42) where the dose was administered (i.e. not missed).
- Per the protocol, participants are expected to receive 2 infusions of Dostarlimab during the 42-day period.
- Participants need to have received at least 2 infusions of Dostarlimab to be considered for DLT-evaluability (in the absence of a DLT during this period)

Treatment exposure will be summarized as follows:

- Number of cycles started summarized as a continuous variable.
- Overall treatment exposure (months), defined as the [(last dose date, data cutoff date) - first dose date + 21] / 30.4375, will be summarize as a continuous variable.
- Actual treatment exposure (months), defined as the overall treatment exposure minus the duration of dose interruptions, will be summarized as a continuous variable.

Treatment compliance will be summarized using study treatment data up to the last dose date by data cut-off date as follows:

- Cumulative dose (mg) is calculated as sum of all actual dose infused.
- Dose intensity (mg/week) is calculated as cumulative dose divided by duration of treatment ([last dose date - first dose date + 21]/7).
- Relative dose intensity (RDI, %) is calculated as dose intensity (mg/week) divided by intended dose intensity (mg/week) multiplied by 100.

- Dose intensity, infusion missing, infusion delay and infusion interruptions will be summarized.

Infusion information for each participant will be presented in a data listing.

4.5.2. Adverse Events

AEs will be collected until 30 days after the last dose of study drug. SAEs will be collected until 90 days after the last dose of study drug (or to a minimum of 30 days after the last dose of study drug if the participant starts alternative anticancer therapy). However, any SAEs assessed as related to study participation or related to study drug will be recorded through the FUP Assessment Period. All AEs and SAEs will be followed until the event is resolved, stabilised, or otherwise explained; until the participant is lost to follow up; or until the participant has died.

AEs will be classified according to current Medical Dictionary for Regulatory Activities (MedDRA). All AEs occurring during the study will be included in by-participant data listings and tabulated by MedDRA system organ class and preferred term. TEAE is defined as any AE with onset after the first administration of study drug, throughout the Treatment Period, until 30 days after cessation of study treatment (or until the start of alternate anticancer therapy, whichever occurs earlier), or any event that was present at baseline but worsened in intensity or was subsequently considered study drug-related by the Investigator through the end of the study. If the start date is missing for an AE and the actual start date cannot be determined from a partial date, the AE will be considered treatment-emergent.

Safety parameters will include the incidence of DLTs, thrombocytopaenia events, TEAEs, related TEAEs, serious TEAEs, TEAEs of Grade 3 or greater by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5 or later, TEAEs leading to death, TEAEs leading to treatment discontinuation, and TEAEs leading to dose modification (interruption, reduction (for niraparib only), and delay (for dostarlimab only)). AESIs and imAE will also be summarised and listed. No formal hypothesis-testing analysis of AE incidence rates will be performed. All AEs occurring on study will be listed in participant data listings. By-participant listings also will be provided for all AEs including SAEs and the reasons for considering as a serious adverse event. Clinical laboratory tests, vital signs, ECG results, performance status, will be summarised and concomitant medication usage will be listed per participant for each assessment. Lising of all laboratory data for subjects with any values of potential clinical importance or outside normal ranges will be provided. Subjects death profiles will be provided.

Related TEAEs are defined as TEAEs related to treatment as judged by the Investigator. Unless otherwise specified, related analysis will be based on related to niraparib, dostarlimab, and any study treatment, respectively.

Any AEs for which the relationship to study drug is missing will be considered as related to study treatment. Within the same MedDRA PT, only the AE with the highest ranked relationship to treatment for each participant will be counted in tabulations by relationship to treatment. Within a MedDRA SOC, participants with more than 1

MedDRA PT will be counted only once for the AE that is most related to treatment. The imputation for a missing relationship will take place prior to determining the most related AE within a SOC or PT for a given participant.

A high-level overview of TEAEs will be presented in a summary table. This table will include the number and percentage of participants for the following categories:

- Any DLTs
- any thrombocytopaenia events
- any TEAE
- any treatment-emergent serious adverse events (TE-SAEs),
- any TEAE and related TEAE leading to deaths

The number and percentage of participants reporting a TEAE will be summarized by SOC, PT, toxicity grade, and relationship to study drug, respectively. AE tabulations will be ordered in terms of decreasing frequency for SOC (alphabetically for SOCs with the same number of AEs reported) and decreasing frequency for PT within SOC (alphabetically for PTs with the same number of AEs reported within a SOC).

The following AE tables and listings will be produced.

- DLTs by SOC and PT (listing)
- Thrombocytopaenia events with toxicity grade 3 or above by SOC and PT (listing)Related TEAE by SOC and PT
- Common (>=5%) TEAE by overall frequency
- Common (>=5%) TEAE and drug related TEAE with toxicity grade 3 or above by overall frequency
- Related TE-SAEs by SOC and PT
- TE-AE with toxicity grade 3 or above by SOC and PT
- Related TE-SAE with toxicity grade 3 or above by SOC and PT
- TEAE and TE-SAE by SOC, PT, and maximum toxicity grade
- Related TEAE by SOC, PT, and maximum toxicity grade
- TEAEs, TE-SAE and related TEAE leading to treatment discontinuation by SOC and PT
- Summary of Common (>=X%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)
- Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency

The following by-participant listings will be produced.

- All AEs

More details will be provided in the Output and Programming Specification (OPS) document.

4.5.2.1. Adverse Events of Special Interest

An adverse event of special interest (AESI) is any AE (serious or nonserious) that is of scientific and medical concern specific to the study drug, for which ongoing monitoring and rapid

communication by the Investigator to the Sponsor is appropriate.

Niraparib AESIs

According to the protocol, AESIs for niraparib are the following:

- myelodysplastic syndrome (MDS) and acute myeloid leukaemia (AML) (MedDRA Criteria for Selection of Preferred Terms: Myelodysplastic syndrome SMQ (Narrow) and Leukaemias acute myeloid (HLT).
- Second primary malignancy (new malignancies [other than MDS or AML]) (MedDRA Criteria for Selection of Preferred Terms: Haematological malignant tumours SMQ (Narrow), Non-haematological malignant tumours SMQ (Narrow)., excluding terms not reflecting a new malignancy, e.g., signs or symptoms of malignancies, disease progression of existing cancer).

The following AESI tables will be produced

- AESI by AESI category and PT
- The AESI SMQ and preferred term list will be provided in the OPS document.

Dostarlimab imAEs

At minimum, the following AE tables will be produced for treatment emergent imAE

- Related imAEs and imSAEs by category , PT, and maximum toxicity grade
- related imAEs leading to treatment discontinuation by SOC and PT
- imAEs will be identified based on a pre-specified search list of preferred terms (PTs) and most recent MedDRA version, documented in a version-controlled repository maintained by GSK and finalized for analysis prior to database lock. Additional Safety Assessments

4.5.2.2. Laboratory Data

Laboratory evaluations including the analyses Haematology laboratory tests, tests will be based on GSK Core Data Standards.

Summary of change from baseline by scheduled visits using mean, median, standard deviation, minimum and maximum will be provided. Unscheduled visits will not be included in summary tables and/or figures, except for worst case summary tables and/or figures.

Summaries of worst-case grade increase from baseline (from both scheduled and unscheduled assessments) grade will be provided for haematology that are gradable by CTCAE v5 or higher. These summaries will display the number and percentage of participants with a maximum post-baseline grade increasing from their baseline grade. Any increase in grade from baseline will be summarized along with any increase to a maximum grade of 3 and any increase to a maximum grade of 4. Missing baseline grade will be assumed as grade 0. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia separately.

For laboratory tests that are not gradable by CTCAE v5 or higher, summaries of worst-case changes from baseline (from both scheduled and unscheduled assessments) with respect to normal range will be generated. Decreases to low, changes to normal or no changes from baseline, and increases to high will be summarized for the worst-case post-baseline. If a participant has a decrease to low and an increase to high during the same time interval, then the participant is counted in both the “Decrease to Low” categories and the “Increase to High” categories. Separate summary tables for haematology tests will be produced.

Listings of liver monitoring/stopping event reporting and hepatobiliary laboratory events including possible Hy’s law cases will be provided in addition to what has been described above. Possible Hy’s Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE.

A by-participant listing of all laboratory for subjects with any value of potential clinical importance / outside normal range will be provided, with laboratory reference ranges and abnormal values highlighted, and including center, participant identifier, and visit. The listings of chemistry, coagulation and liver function laboratory tests will be provided.

Exploratory graphs of laboratory parameters maybe provided.

4.5.2.3. Vital Signs

The change from baseline will be summarized by scheduled visit using mean, median, standard deviation, minimum and maximum.

A by-participant vital sign listing will also be provided.

4.5.2.4. ECG

Standard 12-lead ECGs will be performed using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG will be repeated during the Treatment or Follow-up Periods if clinically indicated.

The QTc values based on Fridericia and Bazett formulas will be rounded to the integer and the values will be categorized into the following CTCAE grade and ranges: Grade 0 (<450 msec), Grade 1 (450-480 msec), Grade 2 (481-500 msec), and Grade 3 (≥501 msec). Summaries of grade increase will be provided. These summaries will display the number and percentage of participants with any grade increase, increase to grade 2 and increase to grade 3 for the worst-case post-baseline only. Missing baseline grade will be assumed as grade 0.

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

A by-participant ECG listing will also be provided.

4.5.2.5. Pregnancies

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

4.6. Other Analyses

4.6.1. Subgroup analyses

For Part 2A and 2B, the primary and secondary efficacy analyses may be performed on participants' CCI [redacted] groups if data is available.

4.7. Interim Analyses

For Part 1 of the study, in accordance with the Sponsors' standard operating procedure, the DEC will monitor intervention-emergent data on an ongoing basis throughout study conduct for the purpose of ensuring the continued safety of participants enrolled in this study as described in detail in the Dose Escalation Plan.

Once all participants in the Safety Run-in have been observed for ≥42 days, all available data from the Part 2 Safety Run-in together with all data previously collected under Protocol Amendment 03 and earlier will be reviewed with the study DEC and the Data Review Committee (DRC) before additional participants on Part 2 are enrolled.

CCI

[redacted]

4.8. Changes to the Protocol Defined Statistical Analysis Plan

Safety Run-In was introduced in the protocol amendment 4. There are no deviations to the originally planned statistical analysis specified in the protocol [(Dated: 12-MAY-2020)].

5. SAMPLE SIZE DETERMINATION

Part 1

Under Protocol Amendment 03, 56 participants in total were planned to be enrolled in Part 1 of the study, this was not based on formal statistical hypotheses but was estimated based on an mTPI-2 dose-escalation design including approximately 7 cohorts (4 cohorts in Part 1A and 3 cohorts in Part 1B) of up to 8 participants each.

A total of 23 participants were enrolled into Part 1A Cohorts 0, 1A, and 1B. Part 1A Cohort 1B was not deemed to be safe, and, as a result, no participants were enrolled into Part 1A Cohort 2. In addition, a total of 3 participants were enrolled into Part 1B Cohort 1, for which enrolment into Part 1B Cohort 1 was prematurely stopped due to DLTs of Grade ≥3 thrombocytopenia.

Under Protocol Amendment 04 and 05, it is anticipated that, 1 to 3 cohorts (up to 8 participants per cohort or approximately 24 participants overall) may be enrolled in Part 1B, unless the incidence of DLTs dictates fewer participants. Additional cohorts (including up to 8 participants per cohort) may be opened in Part 1B if needed to evaluate alternative niraparib dose levels. Lastly, up to 5 additional participants may be enrolled into Part 1B to further evaluate the youngest participant group(s) if not represented. This was not based on formal statistical hypotheses but was estimated based on an mTPI-2 dose-escalation design.

Part 2 Safety Run-in

The statistical gating to initiate Part 2 expansion cohorots will be based on minimum of 8 DLT-evaluable participants for DLTs across osteosarcoma and neuroblastoma. When 2 or less DLTs and 2 or less Grade ≥3 thrombocytopenia AEs are observed, the study will continue to Part 2 Cohort Expansion. When 3 or more DLTs are observed, the study may not continue to Part 2 Cohort Expansion. When 2 or less DLTs and 3 out of 8 Grade ≥3 thrombocytopenia AEs are observed, the study may be paused for data review. This will be the primary guideline for the dose recommendations; the totality of data will be taken

into account. The probability of initiating Part 2 Cohort Expansion and the probability of pausing for data review are presented in Table 6 for 8 DLT-evaluable participants, assuming a weak correlation of 0.15 between the 2 endpoints.

Table 6 Operating characteristics

True DLT Rate	True Grade ≥3 Thrombocytopenia Rate	Probability of Initiating Part 2 Cohort Expansion (2 or Less DLTs and 2 or Less Grade ≥3 Thrombocytopenia Events Observed Out of 8 DLT-evaluable Participants)	Probability of Pausing for Data Review (3 Grade ≥3 Thrombocytopenia Events and 2 or Less DLTs Observed Out of 8 DLT-evaluable Participants)
0.25	0.25	49%	13%
0.30	0.25	40%	10%
0.30	0.30	32%	13%
0.35	0.35	21%	11%
0.45	0.45	6%	6%

If there is a differential in the DLT-evaluable number of participants to 8 for either endpoint, other criteria may apply. Operating characteristics for 9 and 10 participants were evaluated under different observed DLT and Grade ≥3 thrombocytopenia AE events. Below are presented the operating characteristics for the decision guidelines where the operating characteristics were similar to Table 7 and Table 8 results.

Table 7 Operating characteristics for 9 DLT-evaluable participants

True DLT Rate	True Grade ≥3 Thrombocytopenia Rate	Probability of Initiating Part 2 Cohort Expansion (2 or Less DLTs and 3 or Less Grade ≥3 Thrombocytopenia Events Observed Out of 9 DLT-evaluable Participants)	Probability of Pausing for Data Review (4 Grade ≥3 Thrombocytopenia Events and 2 or Less DLTs Observed Out of 9 DLT-evaluable Participants)
0.25	0.25	52%	6%
0.30	0.25	40%	4%
0.30	0.30	36%	7%
0.35	0.35	23%	7%
0.45	0.45	7%	4%

Table 8 Operating characteristics for 10 DLT-evaluable participants

True DLT Rate	True Grade ≥3 Thrombocytopenia Rate	Probability of Initiating Part 2 Cohort Expansion (3 or Less DLTs and 3 or Less Grade ≥3 Thrombocytopenia Events Observed Out of 10 DLT-evaluable Participants)	Probability of Pausing for Data Review (4 Grade ≥3 Thrombocytopenia Events and 3 or Less DLTs Observed Out of 10 DLT-evaluable Participants)
0.25	0.25	62%	11%
0.30	0.25	52%	9%
0.30	0.30	44%	12%
0.35	0.35	29%	12%
0.45	0.45	9%	7%

Part 2A

The sample size for this cohort is based on a Simon's 2-stage optimal design, with a 1-sided alpha of 0.05 and a minimum power of 80%. The null hypothesis is ≤10% PFS6, and the alternative hypothesis is ≥30% PFS6. A futility analysis will be performed after the initial assessment of response for 10 participants in the cohort. If, among the first 10 enrolled participants in the cohort, at least 2 participants remain progression free after 6 months, an additional 19 participants will be enrolled. If 6 or more participants out of the 29 participants enrolled remain progression free after 6 months, the null hypothesis will be rejected. The required sample size of 29 is based on the modified intent-to-treat (mITT) population. The total sample size to be enrolled is planned at up to 30 in case of the potential lack of sufficient participants in the mITT population. Those Part 1 participants who satisfy the inclusion and exclusion criteria of Part 2, satisfy the mITT population definition, and are treated at the dose used in Part 2 will be included in the Part 2 efficacy analysis and will be counted in the required Part 2 sample size. The software for the sample size calculation is PASS 2019 (NCSS, 2019).

Part 2B

The sample size for this cohort is based on a Simon's 2-stage optimal design, with a 1-sided alpha of 0.05 and a minimum power of 80%. The null hypothesis is ≤10% ORR, and the alternative hypothesis is ≥30% ORR. A futility analysis will be performed after the initial assessment of response for 10 participants in the cohort. If, among the first 10 enrolled participants in the cohort, at least 2 participants have objective responses (CR or PR), an additional 19 participants will be enrolled. If 6 or more participants out of the 29 participants enrolled have objective responses, the null hypothesis will be rejected. The required sample size of 29 is based on the modified intent-to-treat (mITT) population. The total sample size to be enrolled is planned at up to 30 in case of the potential lack of sufficient participants in the mITT population. Those Part 1 participants who satisfy the inclusion and exclusion criteria of Part 2, satisfy the mITT population definition, and are treated at the dose used in Part 2 will be included in the Part 2 efficacy analysis and will be counted in the required Part 2 sample size. The software for the sample size calculation is PASS 2019 (NCSS 2019).

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Abbreviations and Trademarks

6.1.1. List of Abbreviations

Abbreviation	Description
CCI [redacted]	
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
BOR	best overall response
CCI [redacted]	
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
Cmax	maximum plasma concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DEC	Dose Escalation Committee
DL-1	dose level -1
DL1	dose level 1
DL2	dose level 2
DLT	dose-limiting toxicity
dMMR	mismatch repair-deficient
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EOT	End of Treatment
FDG-PET	fluorodeoxyglucose-positron emission tomography
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor

Abbreviation	Description
HR	hazard ratio
CCI [redacted]	
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
INRC	International Neuroblastoma Response Criteria
imAE	immune-mediated adverse event
imAEI	immune-mediated adverse event of interest
IRB	Institutional Review Board
IV	intravenous
LAR	legally authorised representative
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	metaiodobenzylguanidine
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MSI-H	high microsatellite instability
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
mTPI-2	modified toxicity probability interval-2
NCI	National Cancer Institute
NE	not evaluable
NIH	National Institutes of Health
ORR	objective response rate
CCI [redacted]	
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PFS	progression-free survival
PFS6	progression-free survival rate at 6 months
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
Q3W	every 3 weeks
QTL	quality tolerance limit
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event

Abbreviation	Description
SAP	statistical analysis plan
SD	stable disease
SOA	schedule of activities
STING	stimulator of interferon genes
t½	half-life
TEAE	treatment-emergent adverse event
tmax	time to maximum plasma concentration
CCI [redacted]	CCI [redacted]
ULN	upper limit of normal
UPM	unit probability mass
WMA	World Medical Association
WOCBP	woman of childbearing potential

6.1.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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MedDRA
NCSS

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