EMADOC-1700519818-2650331
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMA/VR/0000296756

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:
Zejula	Niraparib
JEMPERLI	Dostarlimab

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Submission deadline	14 Nov 2025	22 Oct 2025	
☐	Validation	30 Nov 2025	21 Nov 2025	
☐	Start date	1 Dec 2025	1 Dec 2025	
☐	CHMP Rapporteur AR	12 Jan 2026	13 Jan 2026	
☐	CHMP comments	19 Jan 2026	19 Jan 2026	
☐	Updated CHMP Rapporteur AR	22 Jan 2026	28 Jan 2026	
☐	Request for supplementary information	29 Jan 2026	29 Jan 2026	
	Submission of responses	20 Feb 2026	19 Feb 2026	
☐	Re-start	23 Feb 2026	23 Feb 2026	
☐	CHMP Rapporteur AR	30 Mar 2026	31 Mar 2026	
☐	CHMP comments	13 Apr 2026	13 Apr 2026	
☐	Updated CHMP Rapporteur AR	16 Apr 2026	16 Apr 2026	
☒	CHMP outcome	23 Apr 2026	23 Apr 2026	

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Glaxosmithkline Trading Services Limited submitted to the European Medicines Agency on 22 October 2025 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the Zejula SmPC and sections 4.2, 5.1 and 5.2 of the Jemperli SmPC to include final results from study 213406 (SCOOP). This is a phase 1, multicentre, open-label, dose escalation and cohort expansion study of niraparib and dostarlimab in paediatric participants with recurrent or refractory solid tumours; the Package Leaflet is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/PE/0000270085 for Jemperli and EMA/PE/0000269425 for Zejula on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMA/PE/0000270085 for Jemperli and the PIP EMA/PE/0000269425 for Zejula were completed.

The PDCO issued an opinion on compliance for the PIP EMA/PE/0000270085 for Jemperli and the PIP EMA/PE/0000269425 for Zejula.

2. Overall conclusion and impact on the benefit/risk balance

Niraparib (Zejula) is a Poly [ADP-ribose] polymerase (PARP)-1/2 inhibitor. PARP1 and PARP2 are zinc-finger DNA-binding proteins that detect damaged DNA and promote DNA repair by several mechanisms. Niraparib is approved as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy and for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Dostarlimab (Jemperli) is an anti- programmed cell death protein 1 (PD-1) antibody, a humanized monoclonal antibody (mAb) of the immunoglobulin G4 subclass that binds with high affinity to PD-1 and blocks the interaction between PD-1 and its ligands, programmed cell death-ligand 1 and programmed cell death-ligand 2. Dostarlimab is approved in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent endometrial

cancer (EC) and who are candidates for systemic therapy and as monotherapy for the treatment of adult patients with deficient mismatch repair (dMMR)/ microsatellite instability-high (MSI-H) recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

In accordance with Article 46 of Regulation (EC) No. 1901/2006, the worksharing applicant (WSA) has submitted the final clinical study report (CSR) dated 11 September 2025 for the paediatric study 213406 (SCOOP) which is part of the agreed PIP EMA/PE/0000270085 for Jemperli and the agreed PIP EMA/PE/0000269425 for Zejula.

Study 213406 (SCOOP) was a phase 1, multicenter, open-label, dose escalation and cohort expansion study (two part trial) to evaluate the pharmacokinetics, safety, activity and acceptability of niraparib in combination with dostarlimab in paediatric patients aged 5 to less than 18 years of age with recurrent or refractory (R/R) solid tumours, excluding central nervous system (CNS) tumours in Part 1 (dose-finding) and with R/R osteosarcoma and R/R neuroblastoma in Part 2 (expansion cohorts).

Of note, the study was closed prematurely to further enrolment due to observed toxicities in conjunction with insufficient efficacy. The study was permanently terminated by the target date of 23 April 2025 (Last Subject Last Visit). Consequently, the PIP development was closed too. The results provided with the final CSR of study 213406 (SCOOP) presented safety and efficacy data up to the lock date of 09 June 2025 (end of study analysis).

The paediatric population treated in that study (children aged ≥5 years and adolescents with a median age of 14 years of age) was very limited (N=47) with limited exposure to the combination of niraparib plus dostarlimab (2 months or fewer).

The primary endpoints of the study were dose limiting toxicity (DLTs) by study part and cohort for the DLT evaluable population (Part 1A; Part 1B; Part 2 Safety Run-in), progression-free survival (PFS) at 6 months (PFS6) in Part 2A (Osteosarcoma Expansion Cohort), and objective response rate (ORR) in Part 2B (Neuroblastoma Expansion Cohort) were not achieved.

The efficacy results submitted are very scarce, a response was not reported for any patient (9 patients included in the osteosarcoma expansion cohort, and 8 patients included in the neuroblastoma expansion cohort).

It is agreed with the WSA that no efficacy conclusion for the paediatric population can be drawn from the limited number of paediatric subjects included in study 213406. This is, due to the DLTs and the emergence of safety concerns in the context of any relevant antitumour activity observed, which led to the early termination of the study. Specifically, two paediatric patients developed immune mediated encephalitis and six paediatric patients experienced unmanageable Grade 3-4 thrombocytopenia. Even though these adverse events are not unexpected, because encephalitis and haematological toxicity have been reported with checkpoint inhibitors and PARP 1/2 inhibitors respectively, the severity of the toxicity is considered unacceptable given the lack of efficacy. Consequently, the potential significant therapeutic benefit of this combination of niraparib plus dostarlimab in the paediatric population with recurrent or refractory solid tumours is uncertain.

The types of safety events observed were consistent with the safety profiles of the individual study drugs in adult populations, and no new safety concerns for niraparib or dostarlimab were identified.

The WSA proposed to update sections 4.2, 5.1 and 5.2 of the Jemperli SmPC and to update sections 4.2, 4.8, 5.1 and 5.2 of the Zejula SmPC to reflect the results of the SCOOP study. Following some adjustments to the initially proposed wording, the SmPC changes are considered acceptable for both Jemperli and Zejula

Results obtained in this study does not modify the benefit/risk profile of niraparib and dostarlimab in adults either as monotherapy or as combination therapy.

The benefit-risk balance of Jemperli and zejula remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of sections 4.2, 4.8, 5.1 and 5.2 of the Zejula SmPC and update of sections 4.2, 5.1 and 5.2 of the Jemperli SmPC to include the final results from study 213406 (SCOOP) in order to complete the PIPs EMA/PE/0000270085 for Jemperli and EMA/PE/0000269425 for Zejula and in order to fulfil Article 46 of Regulation EC No 1901/2006. Study 213406 (SCOOP) is a phase 1, multicentre, open-label, dose escalation and cohort expansion study of niraparib and dostarlimab in paediatric participants with recurrent or refractory solid tumours. the Package Leaflet is updated accordingly. In addition, the WSA took the opportunity to implement some minor corrections throughout the Jemperli and the Zejula PIs.

☒ is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan EMA/PE/0000270085 for Jemperli and EMA/PE/0000269425 for Zejula and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet for Jemperli and Zejula.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Jemperli

Section 4.2 'Posology and method of administration'of the SmPC

Paediatric population

The safety and efficacy of JEMPERLI in children and adolescents aged below 18 years of age have not been established. Outside its authorised indications, JEMPERLI in combination with niraparib has been studied in children aged 5 to less than 18 years with recurrent or refractory solid tumours including osteosarcoma and neuroblastoma; however, the study data were limited and the results of the study did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in sections 5.1 and 5.2.

Section 5.1 'Pharmacodynamic properties'of the SmPC

Paediatric population

In a Phase 1 study (SCOOP), the safety, pharmacokinetics, and antitumour activity of JEMPERLI in combination with niraparib were evaluated in 47 children and adolescents with recurrent or refractory solid tumours including osteosarcoma and neuroblastoma. Patients aged 5 to <18 years received JEMPERLI 3 mg/kg or 7.5 mg/kg (up to 500 mg) every 3 weeks.

The study was terminated prematurely due to observed toxicities in conjunction with insufficient efficacy. No efficacy response was observed in the 17 patients with osteosarcoma or neuroblastoma included in the expansion part of the study. The safety profile of the combination in the paediatric population cannot be considered established due to the limited number of paediatric patients evaluated with limited exposure. See section 4.2 for information on paediatric use.

Section 5.2 'Pharmacokinetic properties'of the SmPC

Paediatric population

In a Phase 1 study (SCOOP), the pharmacokinetics of dostarlimab was evaluated in 44 children and adolescents with recurrent or refractory solid tumours. The study was prematurely terminated and therefore the pharmacokinetic data obtained were limited. In the participant samples analysed at 7.5 mg/kg (N = 28), dostarlimab exposures were generally consistent with those seen in adults.

Zejula

Section 4.2 'Posology and method of administration'of the SmPC

Paediatric population

The safety and efficacy of Zejula in children and adolescents aged below 18 years of age have not been established. Outside its authorised indications, Zejula in combination with dostarlimab has been studied in children aged 5 to less than 18 years with recurrent or refractory solid tumours including osteosarcoma and neuroblastoma; however, the study data were limited and the results of the study did not allow to conclude that the benefits of such use outweigh the risks. Currently available data are described in sections 5.1 and 5.2.

Section 5.1 'Pharmacodynamic properties'of the SmPC

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Zejula in all subsets of the paediatric population in ovarian carcinoma, excluding rhabdomyosarcoma and germ cell tumours (see section 4.2 for information on paediatric use). However, paediatric development was conducted in children and adolescents with other oncology conditions.

In a Phase 1 study (SCOOP), the safety, pharmacokinetics, and antitumour activity of Zejula in combination with dostarlimab were evaluated in 47 children and adolescents with recurrent or refractory solid tumours including osteosarcoma and neuroblastoma. Patients aged 5 to <18 years received Zejula 75 to 200 mg daily.

The study was terminated prematurely due to observed toxicities in conjunction with insufficient efficacy. No efficacy response was observed in the 17 patients with osteosarcoma or neuroblastoma included in the expansion part of the study. The safety profile of the combination in the paediatric population cannot be considered established due to the limited number of paediatric patients evaluated with limited exposure. See section 4.2 for information on paediatric use.

Section 5.2 'Pharmacokinetic properties'of the SmPC

Paediatric population

In a Phase 1 study (SCOOP), the pharmacokinetics of niraparib was evaluated in 44 children and adolescents with recurrent or refractory solid tumours. While a clinical study was initiated to evaluate pharmacokinetics in this population, the study was prematurely terminated. Consequently, the pharmacokinetic data obtained were limited and insufficient to reliably characterise exposures in paediatric patients.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Niraparib (Zejula) is a PARP-1/2 inhibitor. PARP1 and PARP2 are zinc-finger DNA-binding proteins that detect damaged DNA and promote DNA repair by several mechanisms. Niraparib is approved as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy and for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

Dostarlimab (Jemperli) is an anti-PD-1 antibody, a humanized mAb of the immunoglobulin G4 subclass that binds with high affinity to PD-1 and blocks the interaction between PD-1 and its ligands, programmed cell death-ligand 1 and programmed cell death-ligand 2. Dostarlimab is approved in combination with carboplatin and paclitaxel for the first-line treatment of adult patients with primary advanced or recurrent EC and who are candidates for systemic therapy and as monotherapy for the treatment of adult patients with dMMR/MSI-H recurrent or advanced EC that has progressed on or following prior treatment with a platinum-containing regimen.

As part of this variation application the WSA has submitted a paediatric study for Zejula (niraparib) and Jemperli (dostarlimab), study 213406 (SCOOP), in accordance with Article 46 of Regulation (EC) No 1901/2006 as amended. The SCOOP study is a clinical measure of the agreed Paediatric Investigation Plan (PIP) for dostarlimab (EMA/PE/0000270085) and niraparib (EMA/PE/0000269425). Of note, the study was closed to further enrolment due to observed toxicities in conjunction with insufficient efficacy. An update to the SmPC for both products is proposed by the WSA to reflect the results from the SCOOP study. No change to the indication, posology, pharmaceutical form/formulation, or route of administration is proposed by the WSA for both products. In addition the WSA took the opportunity to implement small corrections throughout the PI for both products.

6. Clinical Pharmacology aspects

SCOOP study is a phase 1, multicenter, open-label, dose escalation and cohort expansion study of niraparib and dostarlimab in pediatric patients with recurrent or refractory solid tumors. Dose escalation was planned in Part 1A and Part 1B of the study to consist of multiple dose level cohorts. Dose expansion was planned in Part 2A (osteosarcoma) and Part 2B (neuroblastoma).

The study was closed to further enrollment on 10 March 2025 and permanently terminated on 23 April 2025 (Last Participant Last Visit) due to observed toxicities in conjunction with insufficient efficacy of the niraparib and dostarlimab combination in pediatric participants. Due to the early termination of the study, Part 1B of the study only enrolled 3 participants, with the youngest being 5 years old.

6.1. Methods – analysis of data submitted

The secondary objectives of this study were the characterization of the PK of the combination of niraparib and dostarlimab in pediatric participants and the assessment of the immunogenicity of dostarlimab in pediatric participants.

Study participants

A total of 50 participants were screened; 47 participants were treated in this study. A total of 7 populations were used in the analysis of data for this clinical study. The number of participants included in each population is provided in the table below.

Table 1 Study Populations

Population, n (%)	Part 1A (N=23)	Part 1B (N=3)	Part 2A (N=11)	Part 2B (N=7)	Part 2 Safety Run-In (N=3)
Screened[a]	23	3	11	7	3
Safety	23	3	11	7	3
Intent-to-Treat	22	3	NA	NA	NA
Modified Intent-to-Treat	NA	NA	9[b]	8[b]	3
DLT-evaluable	16	2	NA	NA	3
Pharmacokinetic	23	3	11	7	3
Immunogenicity	23	3	11	7	3

Abbreviations: DLT=dose-limiting toxicity; NA=not applicable; SAP=Statistical Analysis Plan.
Note: Subjects are included in the Safety Population if they had taken at least one dose of study treatment.
Note: For key definitions of each population, see the SAP, Section 3.
Source: Table 1.1, Table 1.4, Table 2.1, Table 2.4, Table 3.3, Table 4.1, Table 5.1
a. Three participants in the Screened population were not assigned to any cohort.
b. Those Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfied the mITT population definition, and were treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis.

There were three participants in the Screened population who were not assigned to any cohort. The Intention-to-Treat population was used for the analysis of Part 1 and modified Intention-to-Treat population was used in the analysis of the efficacy endpoints in Part 2.

See the below table for a summary of Demographic Characteristics and Disease Characteristics.

Table 2 Summary of Demographic Characteristics and Disease Characteristics at Initial Diagnosis (Screened Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3	Total N=50
Sex								
n	11	7	5	3	11	7	3	50
Female	1 (9)	5 (71)	3 (60)	3 (100)	5 (45)	3 (43)	2 (67)	24 (48)
Male	10 (91)	2 (29)	2 (40)	0	6 (55)	4 (57)	1 (33)	26 (52)
Age (YEARS)								
n	11	7	5	3	11	7	3	50
Mean (SD)	13.9 (2.84)	13.7 (3.99)	13.0 (3.81)	6.0 (1.0)	14.3 (2.45)	10.1 (2.97)	14.7 (1.53)	12.9 (3.50)
Median	15.0	15.0	14.0	6.0	14.0	10.0	15.0	14.0
Min	9	9	9	5	10	7	13	5
Max	17	18	17	7	17	15	16	18
Weight (kg)								
n	11	7	5	3	11	7	3	47
Mean (SD)	47.6 (14.78)	47.1 (23.54)	64.5 (22.93)	18.6 (1.70)	55.8 (17.01)	36.1 (12.63)	50.2 (24.45)	47.9 (19.95)
Median	51.0	38.2	65.0	17.7	59.2	39.0	44.0	45.2
Min	23	20	41	18	25	21	30	18
Max	68	92	97	21	83	51	77	97
Karnofsky Scale								
n	2	3	1	0	3	0	0	9
Mean (SD)	80.0 (14.14)	96.7 (5.77)	100.0 (NA)	NA	96.7 (5.77)	NA	NA	93.3 (10.00)
Median	80.0	100.0	100.0	NA	100.0	NA	NA	100.0
Min	70	90	100	NA	90	NA	NA	70
Max	90	100	100	NA	100	NA	NA	100
Lansky Scale								
n	9	4	4	3	8	7	3	38
Mean (SD)	93.3 (8.66)	92.5 (9.57)	92.5 (5.00)	96.7 (5.77)	85.0 (11.95)	94.3 (11.34)	90.0 (17.32)	91.6 (10.27)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3	Total N=50
Median	100.0	95.0	90.0	100.0	85.0	100.0	100.0	95.0
Min	80	80	90	90	70	70	70	70
Max	100	100	100	100	100	100	100	100
Tumor Type								
Osteosarcoma	5 (45)	1 (14)	3 (60)	0	11 (100)	0	3 (100)	NA
Neuroblastoma	0	3 (43)	0	3 (100)	0	7 (100)	0	NA
Adrenocortical carcinoma	0	1 (14)	0	0	0	0	0	NA
Ewing sarcoma	5 (45)	1 (14)	1 (20)	0	0	0	0	NA
Rhabdomyosarcoma	1 (9)	1 (14)	1 (20)	0	0	0	0	NA
Stage of Tumor at Screening								
Stage IV	10 (91)	7 (100)	5 (100)	3 (100)	7 (64)	7 (100)	3 (100)	NA
Stage IVA	0	0	0	0	2 (18)	0	0	NA
Stage IVB	1 (9)	0	0	0	1 (9)	0	0	NA
Missing	0	0	0	0	1 (9)	0	0	NA
Time since Initial Diagnosis (Months)								
n	11	7	5	3	11	7	3	NA
Mean (SD)	33.93 (23.319)	50.20 (50.094)	24.80 (10.948)	39.49 (8.265)	23.16 (14.332)	55.11 (36.823)	19.58 (9.181)	NA
Median	24.48	41.43	27.66	41.89	22.11	58.87	22.01	NA
Q1	17.22	12.58	17.05	30.29	11.73	19.84	9.43	NA
Q3	62.06	72.90	31.67	46.29	30.49	71.39	27.30	NA
Min	5.5	6.6	10.3	30.3	6.2	17.5	9.4	NA
Max	72.8	148.8	37.3	46.3	55.7	124.0	27.3	NA
Line of Anticancer Therapy								
1	1 (9)	1 (14)	0	0	1 (9)	0	0	NA
2	6 (55)	1 (14)	3 (60)	0	8 (73)	1 (14)	3 (100)	NA
3	2 (18)	2 (29)	1 (20)	0	2 (18)	2 (29)	0	NA

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3	Total N=50
4	1 (9)	0	1 (20)	2 (67)	0	2 (29)	0	NA
≥5	1 (9)	3 (43)	0	1 (33)	0	2 (29)	0	NA
Best Response for Last Anticancer Therapy								
Complete response	4 (36)	4 (57)	2 (40)	2(67)	4 (36)	3 (43)	0	NA
Very good partial response	1 (9)	0	0	0	0	0	0	NA
Partial response	4 (36)	1 (14)	2 (40)	1 (33)	0	3 (43)	2 (67)	NA
Minimal response	0	0	0	0	0	0	1 (33)	NA
Stable disease	2 (18)	1 (14)	1 (20)	0	1 (9)	1 (14)	0	NA
Progressive disease	0	1 (14)	0	0	6 (55)	0	0	NA

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation; Max=Maximum; Min=Minimum; NA=not applicable; Q1=first quarter; Q3=third quarter; SD=standard deviation; TfOS=Tablet for Oral Suspension.

[1] Participant in Part 1A Cohort 1A age 18 at consent: participant was <18 years of age at consent and hence met all eligibility criteria. Reason: the clinical database standardly records first of the month for the day of birth as the real day of birth is not recorded for subject confidentiality; therefore this led to discrepancy between the real and the recorded date of birth and age at consent.

Under Protocol Amendment 03, a total of 23 participants were treated in Part 1A: Cohorts 0, 1A, and 1B. Part 1A: Cohort 1B was not deemed to be safe, and, therefore, no participants were enrolled into Part 1A: Cohort 2. In addition, 3 participants were treated in Part 1B: Cohort 1, into which enrollment was prematurely stopped due to AEs of Grade ≥3 thrombocytopenia. For the Part 2 Cohort Expansion, a total of 11 participants were treated in the osteosarcoma cohort (Part 2A), and a total of 7 participants were treated in the neuroblastoma cohort (Part 2B) prior to the pause of enrollment due to AEs of Grade ≥3 thrombocytopenia.

Under Protocol Amendment 04, 3 participants were treated in the Part 2 Safety Run-in. No participants were treated in Part 1B.

Of the 50 participants in the Screened population, no participants were ongoing in Part 1 or Part 2 at the time of DBL and no participants had completed the study, all participants were discontinued from the study overall.

A participant was considered to have completed the study if the participant had completed all study assessments. The most common primary reasons for study discontinuation overall were death (40.0% participants) and participant reaching protocol-defined stopping criteria (36.0% participants).

A participant was considered to have reached protocol-defined stopping criteria if the participant had started alternative anticancer therapy or had met liver chemistry or QTc stopping criteria.

Analytical Methods

The validated ELISA method for quantifying dostarlimab in human serum has previously been assessed and found acceptable in previous procedures, with cross-validation confirming comparable performance at another site. In the current submission, partial validation demonstrated robust long-term stability of dostarlimab in human serum at –80°C for up to 2,981 days, with all calibration standards and QC samples meeting acceptance criteria.

For niraparib and M1, validated LC-MS/MS methods and cross-validation confirmed adequate analytical quantification and comparability between sites. In this application, partial validation prior to study 213406 has been performed to demonstrate extended long-term stability in human plasma for at least 2,134 days at -80°C, with additional stability confirmed after multiple freeze/thaw cycles and short-term storage.

PK Analysis

The PK characteristics of niraparib and dostarlimab were evaluated in the PK Population of this study using sparse blood sampling and population PK approaches. 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.

Serum concentrations of dostarlimab and plasma concentrations of niraparib and its M1 metabolite are presented using descriptive statistics by dose cohort and overall. Summary statistics include mean, standard deviation, coefficient of variation (CV), geometric mean, geometric mean CV, median, and minimum and maximum values.

The niraparib M1 metabolite concentration data was planned to be used to evaluate the age-related development of niraparib metabolism in paediatric participants, if data permit. Niraparib and dostarlimab concentration-time data were analysed using a population approach. A nonlinear mixed effects model was used to determine population pharmacokinetic parameters and identify relevant covariates (e.g. age, weight, or disease-related covariates). The data from this study were combined with data from other studies.

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) was planned tobe explored using population modelling approaches. If data permit, the effects of covariates was planned to be explored.

Niraparib pharmacokinetics:

The PK of niraparib was evaluated in the PK population of the SCOOP study using sparse blood sampling. Blood samples for plasma niraparib were collected during Cycle 1 Day 1 at approximately 2.5 hrs, 7 hrs, and 168 hrs (predose Cycle 1 Day 8) after the first dose and at predose on Cycle 2 Day 1 and Cycle 2 Day 1 at 5 hours after niraparib dose.

PK data from a total of 44 participants enrolled as of July 2023 were assessed by comparing SCOOP pediatric data with those of adults receiving niraparib at either a 200 mg daily dose or an individualized starting dose (300 mg QD for adult participants with a baseline body weight =77 kg and baseline platelet count =150 000/µL and 200 mg QD dosing for adult participants with a baseline body weight <77 kg or baseline platelet count <150 000/µL).

Adult model-based predicted concentration-time profiles were based on the PRIMA 2021 niraparib adult model based on data from studies PN001, NOVA, PRIMA, and QUADRA. The final population PK model was a three-compartment model with linear elimination, with a constant (i.e. zero-order) rate of drug release into the absorption compartment preceded by a Tlag and followed by first-order absorption into the central compartment. Model-predictions were performed for all participants in NOVA, QUADRA, and PRIMA studies (N=1338) using their post hoc PK parameter estimates.

Dostarlimab pharmacokinetics:

The PK of dostarlimab was evaluated in the PK population of the SCOOP study using sparse blood sampling. Blood sampling to assess dostarlimab PK and dostarlimab ADA and NAbs was conducted during the SCOOP study. Ad hoc exploratory analyses of dostarlimab in pediatric participants were undertaken using serum concentration data for dostarlimab from Part 1A, Part 1B, and Part 2 of the SCOOP study, utilizing previously developed population PK models of dostarlimab.

Blood samples for serum dostarlimab PK and/or ADA and NAb were collected during Cycle 1 Day 1 at the following time points relative to the start of the dostarlimab infusion: Cycle 1 Day 1 at Predose (PK, ADA, NAb) and 1 hour post-dose (PK only), Cycle 1 Day 8 at 168 hr post-first dostarlimab dose (PK, ADA, NAb), and predose on Cycle 2 Day 1 at 504 hr post-first dostarlimab dose (PK, ADA, NAb).

Blood samples for serum dostarlimab PK, anti-drug antibodies (ADA), and neutralising antibodies (Nab) were also collected at the following time periods: predose in Cycles 4 and 6, every 6 cycles thereafter up to 2 years, end of treatment (EOT) Visit, 30-day Safety follow-up (FUP) Visit.

Adult model-based predicted concentration-time profiles were based on the final population PK model for the GARNET study. Covariate distributions for simulations were obtained by resampling with replacement from the GARNET study population (N=548). This reference population consists of adults ranging in age from 24 to 86 years.

The final GARNET population PK model was used to simulate 1000 virtual patients using a dosing regimen of 500 mg dostarlimab Q3W for adults (the approved Cycle 1 adult dose). Simulations of 1000 virtual patients were used to derive 95% prediction intervals (i.e. from the 2.5t^{h} to the 97.5th percentile of the simulated values at each timepoint). Simulations included inter-individual variability but did not include parameter uncertainty or residual error. Plots were created by plotting observed dostarlimab PK concentration-time data for Cycle 1 of the SCOOP study 7.5 mg/kg Q3W cohorts overlaid on the simulation-derived 95% PI.

Immunogenicity Analysis

Immunogenicity of dostarlimab was analysed only in the Immunogenicity (ADA) Population. The ADA Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

Minimally, ADA will be evaluated in all predose samples collected at each specified time point, as well as at EOT, at the Safety Follow-up Visit (30 days post-treatment), and at the first Follow-up Visit (90 days post-treatment). The number and percent of participants who become positive for ADAs and who develop NAb were summarised by treatment, visit/time and overall.

Method validation

The validated electrochemiluminescence (ECL) method bridging immunogenicity assay, as found in a submitted report, reliably detects anti-drug antibodies in human serum. This method was already assessed in previous procedures, and demonstrated adequate specificity, sensitivity, precision, and robustness. No hook effect was observed. Validation samples were stable for at least 850 days at -80ºC. Drug and target tolerance were confirmed. A cross-validation was performed to demonstrate acceptable performance when the method was transferred between sites.

The validated SPEAD ECL immunoassay is used for detecting neutralizing anti-GSK4057190 antibodies in human serum. The assay uses competitive ligand binding with biotinylated PD-L1 and Sulfo-Tag-labeled GSK4057190, demonstrating acceptable precision, specificity, stability, and tolerance, supporting its suitability for clinical sample analysis.

6.2. Results

Sample analysis

The bioanalytical study report details the method performance for dostarlimab quantification in study 213406. A total of 453 samples (249 PK and 204 ADA) were received and analyzed across 23 runs between May 2021 and April 2025, with no rejected runs. The validated method demonstrated robust performance, with all PK samples analyzed within the validated stability period (up to 1,477 days at –80°C) and no hook effect observed at concentrations up to 1,500 µg/mL. Calibration curves and QC samples met acceptance criteria for accuracy and precision, and incurred sample reanalysis (ISR) confirmed method reliability.

For niraparib and its metabolite M1, method performance is described in a report. A total of 282 plasma samples were received, with 142 analyzed as primary samples in 12 analytical runs between April 2021 and January 2025. The validated LC-MS/MS method covered a range in ng/mL, and all accepted runs met predefined accuracy and precision criteria for both calibration standards and QC samples. The maximum storage period at –80°C was within the validated long-term stability timeframe (2,134 days).

Quality control procedures were applied in both assays. For dostarlimab, calibration curves included eight standard levels and QCs at three concentrations, with acceptance criteria met in all runs. For niraparib

and M1, calibration curves included nine standard levels and QCs at three or four concentrations per run. ISR was performed for both analytes, with 100% of niraparib and 93.8% of M1 samples meeting acceptance criteria; one minor deviation was noted but did not impact study integrity.

Overall, the analytical methods for dostarlimab, niraparib, and M1 were robust, with all key performance parameters—accuracy, precision, stability, and reliability—demonstrated in accordance with regulatory expectations. The results support the suitability of these methods for the quantification of study analytes in clinical samples from study 213406.

Niraparib pharmacokinetics results:

The overlay plot of observed pediatric data with simulated adult concentration-time profiles after 200 mg QD niraparib is presented in the figure below, and summary concentration data at each time point for pediatric and adult participants are presented in the below table.

Figure 1 Overlay of observed pediatric data by time point (colored dots) for each cohort on simulated adult concentration-time profiles receiving 200 mg QD niraparib from 0 to 168 hours post-dose presented on linear (A) and semilogarithmic (B) scales.

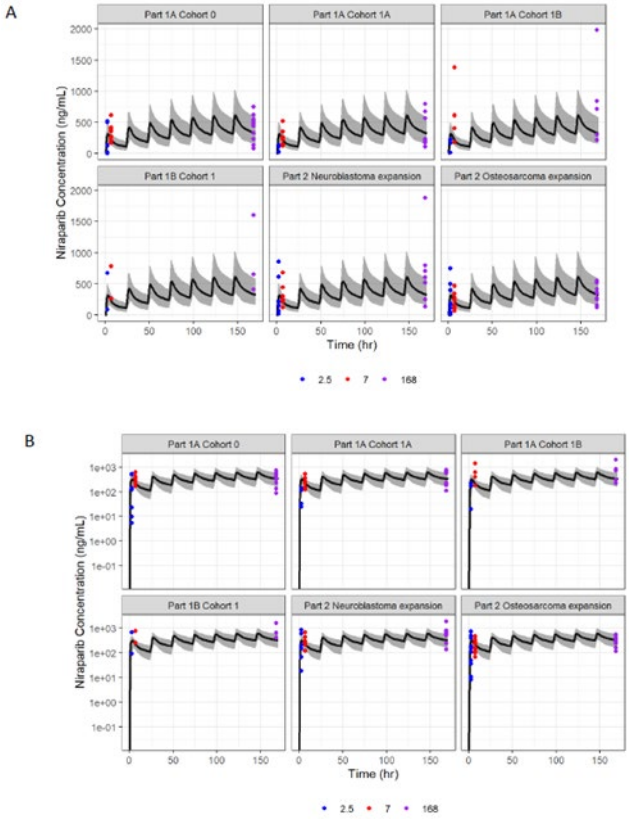


Table 3 Comparison of summary statistics (observed paediatric data by cohort vs. simulated adult data) for concentrations (ng/mL) at 2.5, 7, and 168 hours (200 mg QD niraparib dosing for simulations of adult participants)

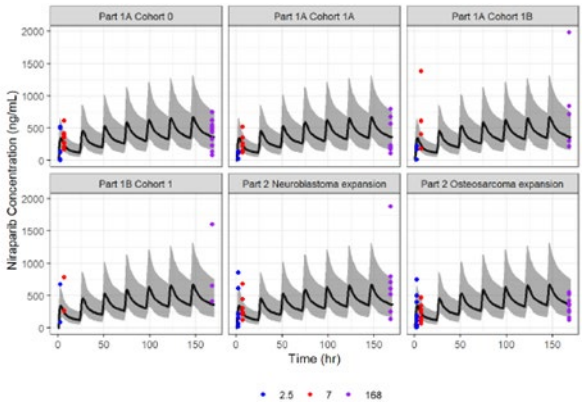
Data	Cohort	Time (hr)	N	Mean (SD); Median [Minimum, Maximum]
Prediction	-	2.5	1338	308.9 (107.3); 313 [5.4, 776.6]
Observed	Part 1A Cohort 0	2.5	7	188.6 (225.1); 124 [5.4, 518]
Observed	Part 1A Cohort 1A	2.5	4	77.5 (57.5); 73.1 [24.9, 139]
Observed	Part 1A Cohort 1B	2.5	3	139.1 (107.1); 172 [19.4, 226]
Observed	Part 1B Cohort 1	2.5	2	383.9 (413.1); 383.9 [91.8, 676]
Observed	Part 2 Neuroblastoma expansion	2.5	6	321.5 (337.2); 184 [18.9, 857]
Observed	Part 2 Osteosarcoma expansion	2.5	11	217.2 (236.6); 154 [8.1, 751]
Prediction	-	7	1338	224.1 (53.2); 222 [26.1, 665.3]
Observed	Part 1A Cohort 0	7	9	347.9 (134); 357 [171, 616]
Observed	Part 1A Cohort 1A	7	7	254.6 (141.7); 227 [125, 518]
Observed	Part 1A Cohort 1B	7	5	640.2 (449.6); 612 [187, 1380]
Observed	Part 1B Cohort 1	7	2	522.5 (369.8); 522.5 [261, 784]
Observed	Part 2 Neuroblastoma expansion	7	7	329.6 (182.8); 303 [124, 679]
Observed	Part 2 Osteosarcoma expansion	7	11	241.5 (143.4); 236 [67.1, 474]
Prediction	-	168	1338	347.1 (115.9); 334.4 [73, 1268.3]
Observed	Part 1A Cohort 0	168	11	419.3 (203.6); 474 [86.8, 749]
Observed	Part 1A Cohort 1A	168	7	396.3 (276.8); 233 [112, 795]
Observed	Part 1A Cohort 1B	168	5	812 (704.6); 714 [219, 1980]
Observed	Part 1B Cohort 1	168	3	887.7 (628.4); 651 [412, 1600]
Observed	Part 2 Neuroblastoma expansion	168	7	700.1 (571.7); 606 [137, 1880]
Observed	Part 2 Osteosarcoma expansion	168	10	354.1 (153.8); 358.5 [120, 555]

hr: hour, SD: standard deviation.

The overlay plot of observed pediatric data with simulated adult concentration-time profiles after an individualized starting dose of niraparib (200 mg QD or 300 mg QD based on baseline body weight and platelet count) is presented in the below figure and summary concentration data at each time point for pediatric and adult participants are presented in the below table.

Figure 2 Overlay of observed pediatric data by time point (colored dots) for each cohort on simulated adult concentration profiles receiving 200 mg QD or 300 mg QD niraparib based on baseline weight and baseline platelet thresholds from 0 to 168 hours post dose presented on linear (A) and semilogarithmic (B) scales

A



B

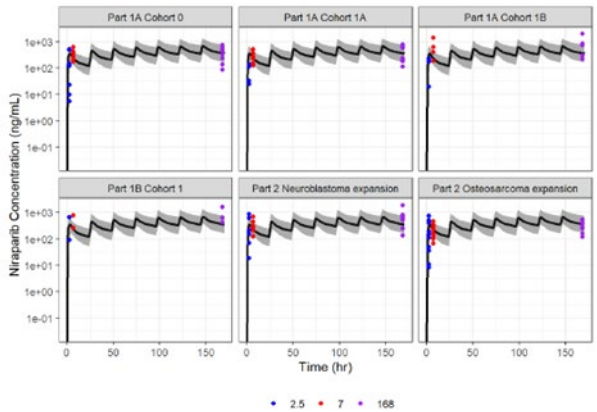


Table 4 Comparison of summary statistics (observed pediatric data by cohort vs. simulated adult data) for concentrations (ng/mL) at 2.5, 7, and 168 hours (200 mg QD or 300 mg QD niraparib dosing based on baseline weight and baseline platelet thresholds for simulations of adult participants)

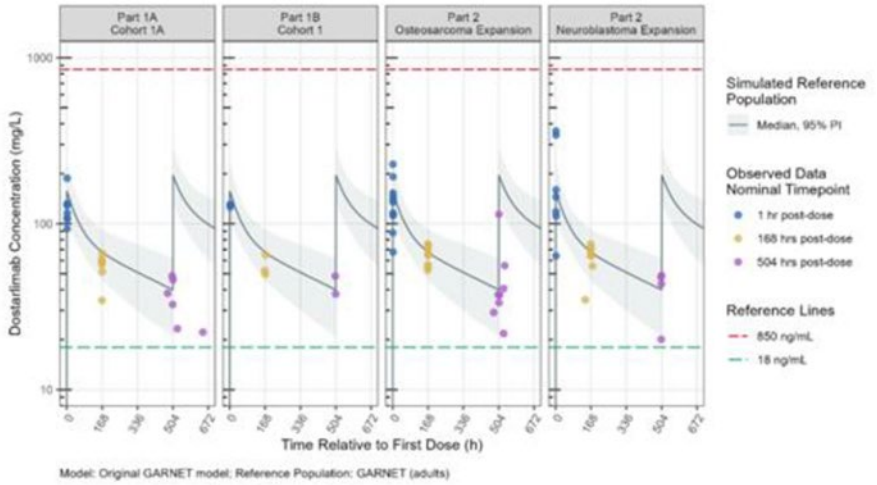
Data	Cohort	Time (hr)	N	Mean (SD); Median [Minimum, Maximum]
Prediction	-	2.5	1338	351.5 (142.6); 340 [5.4, 1000.3]
Observed	Part 1A Cohort 0	2.5	7	188.6 (225.1); 124 [5.4, 518]
Observed	Part 1A Cohort 1A	2.5	4	77.5 (57.5); 73.1 [24.9, 139]
Observed	Part 1A Cohort 1B	2.5	3	139.1 (107.1); 172 [19.4, 226]
Observed	Part 1B Cohort 1	2.5	2	383.9 (413.1); 383.9 [91.8, 676]
Observed	Part 2 Neuroblastoma expansion	2.5	6	321.5 (337.2); 184 [18.9, 857]
Observed	Part 2 Osteosarcoma expansion	2.5	11	217.2 (236.6); 154 [8.1, 751]
Prediction	-	7	1338	254.9 (79.1); 237.4 [26.1, 665.3]
Observed	Part 1A Cohort 0	7	9	347.9 (134); 357 [171, 616]
Observed	Part 1A Cohort 1A	7	7	254.6 (141.7); 227 [125, 518]
Observed	Part 1A Cohort 1B	7	5	640.2 (449.6); 612 [187, 1380]
Observed	Part 1B Cohort 1	7	2	522.5 (369.8); 522.5 [261, 784]
Observed	Part 2 Neuroblastoma expansion	7	7	329.6 (182.8); 303 [124, 679]
Observed	Part 2 Osteosarcoma expansion	7	11	241.5 (143.4); 236 [67.1, 474]
Prediction	-	168	1338	394.8 (152.5); 364.3 [73, 1268.3]
Observed	Part 1A Cohort 0	168	11	419.3 (203.6); 474 [86.8, 749]
Observed	Part 1A Cohort 1A	168	7	396.3 (276.8); 233 [112, 795]
Observed	Part 1A Cohort 1B	168	5	812 (704.6); 714 [219, 1980]
Observed	Part 1B Cohort 1	168	3	887.7 (628.4); 651 [412, 1600]
Observed	Part 2 Neuroblastoma expansion	168	7	700.1 (571.7); 606 [137, 1880]
Observed	Part 2 Osteosarcoma expansion	168	10	354.1 (153.8); 358.5 [120, 555]

SD, Standard deviation.

Dostarlimab pharmacokinetics results:

At the time of the pause in enrollment in July 2023, there were a total of 28 participants in the SCOOP study dosed at 7.5 mg/kg Q3W. All participants had at least 1 dostarlimab PK sample collected. The below figure shows a plot of observed dostarlimab PK concentration-time data for Cycle 1 of the SCOOP study for the 7.5 mg/kg (capped at 500 mg) Q3W cohorts (N=28) overlaid on 95% PI for 1000 simulated virtual patients using the GARNET population PK model. Data from participants in Cohort 0 and Cohort 1B in Part 1A of the study who received dostarlimab at 3 mg/kg Q3W were not included in the analysis.

Figure 3 Overlay of Cycle 1 observed dostarlimab PK concentration-time data from the SCOOP study 7.5 mg/kg Q3W cohorts with 95% prediction intervals for dostarlimab in the GARNET study adult reference population, simulated according to the GARNET model



Note: Green dashed line is the EC90 for IL-2 stimulation (18 mg/L); red dashed line is the maximum observed concentration included in the GARNET population PK analysis (850 mg/L).

All observed dostarlimab PK concentrations for participants in Part 1A and Part 2 (osteosarcoma and neuroblastoma expansions) receiving 7.5 mg/kg Q3W in Cycle 1 of the SCOOP study were above 18 mg/L, the EC90 for IL-2 stimulation by dostarlimab.

Most of the observed concentrations for dostarlimab fell within the 95% PI. The exploratory analysis demonstrated that observed dostarlimab exposures in pediatric participants following 7.5 mg/kg (up to 500 mg) Q3W dosing are consistent with model predicted exposure ranges for adults receiving the approved dose regimen for dostarlimab of 500 mg Q3W.

Immunogenicity

Dostarlimab immunogenicity was assessed using a risk-based bioanalytical strategy to understand whether ADA responses against dostarlimab impact safety, efficacy or PK. Based on the low immunogenicity risk for dostarlimab, a validated, multi-tiered approach to evaluating anti-dostarlimab antibodies, consisting of screening, confirmation, titration, and neutralizing assays was implemented.

All 47 participants who were treated with dostarlimab had at least one immunogenicity sample with a result and were included in the Immunogenicity Population (see table below). One participant did not have baseline ADA results.

The observed incidence of post-treatment ADA to dostarlimab was very low. None of the 46 participants with available baseline ADA results had treatment-induced ADA or treatment-boosted ADA for an overall incidence of treatment-emergent ADA of 0.0%. There were 9 participants (20%) with

treatment-unaffected ADA (pre-existing ADA at baseline with no meaningful increase in titer post-dose). Forty-six participants were classified as negative for treatment-emergent ADAs.

Table 5 Immunogenicity Incidence and Summary - Dostarlimab

	Part 1A: Cohort 0 Niraparib Tablet 100mg/ Dostarlimab 3mg/kg (N=11)	Part 1A: Cohort 1A Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=7)	Part 1A: Cohort 1B Niraparib Tablet 200mg/ Dostarlimab 3mg/kg (N=5)
Subjects with baseline Anti-drug Antibody (ADA) results	11	7	5
Baseline Positive ADA	2 (18%)	4 (57%)	0
Baseline Negative ADA	9 (82%)	3 (43%)	5 (100%)
Subjects with any post-baseline ADA results	11	7	5
ADA Negative [1]	11 (100%)	7 (100%)	5 (100%)
Treatment-unaffected ADA [2]	2 (18%)	4 (57%)	0
Treatment-emergent ADA (Incidence) [3]	0	0	0
Treatment-induced ADA [4]	0	0	0
Titer value [5]			
Min.			
Median			
Max.			
Treatment-boosted ADA	0	0	0
Titer value [5]			
Min.			
Median			
Max.			

	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ Dostarlimab 7.5mg/kg (N=3)	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=11)	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=7)
Subjects with baseline Anti-drug Antibody (ADA) results	3	10	7
Baseline Positive ADA	0	1 (10%)	1 (14%)
Baseline Negative ADA	3 (100%)	9 (90%)	6 (86%)
Subjects with any post-baseline ADA results	3	10	7
ADA Negative [1]	3 (100%)	10 (100%)	7 (100%)
Treatment-unaffected ADA [2]	0	1 (10%)	1 (14%)
Treatment-emergent ADA (Incidence) [3]	0	0	0
Treatment-induced ADA [4]	0	0	0
Titer value [5]			
Min.			
Median			
Max.			
Treatment-boosted ADA	0	0	0
Titer value [5]			
Min.			
Median			
Max.			

	Part 2: Safety Run-In Niraparib TfOS (weight-based dose)/ Dostarlimab 7.5mg/kg (N=3)	Total (N=47)
Subjects with baseline Anti-drug Antibody (ADA) results	3	46
Baseline Positive ADA	1 (33%)	9 (20%)
Baseline Negative ADA	2 (67%)	37 (80%)
Subjects with any post-baseline ADA results	3	46
ADA Negative [1]	3 (100%)	46 (100%)
Treatment-unaffected ADA [2]	1 (33%)	9 (20%)
Treatment-emergent ADA (Incidence) [3]	0	0
Treatment-induced ADA [4]	0	0
Titer value [5]		
Min.		
Median		
Max.		
Treatment-boosted ADA	0	0
Titer value [5]		
Min.		
Median		
Max.		

Abbreviations: AAOLF = Age-appropriate Oral Liquid Formulation, TfOS = Tablet for Oral Suspension.
Note: The denominator for baseline section is the number of subjects with baseline ADA results; for post-baseline section it is the number of subjects with any post-baseline ADA results.
[1] Trt-unaffected subjects, or subjects without a trt-induced or trt-boosted ADA at any time during the treatment period or follow-up. [2] ADA positive at baseline and titer remained <= 4x baseline titer post-baseline or were ADA negative. [3] Trt-induced or trt-boosted ADA.[4] Baseline negative or missing and post-baseline confirmed positive. [5] Subjects may contribute more than one titer value.
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Method performance of immunogenicity sample analysis

A report describes the anti-drug antibody (ADA) analytical performance results. It includes all results of all samples collected up to the data cut-off date of 28 March 2025.

Samples were analyzed in 21 runs, with storage at –80°C and thawing at room temperature prior to analysis. All analyses were performed within validated stability parameters. The minimum required dilution was 1:4 in Low Cross buffer, with further dilution for titer assays. Quality control samples were included in all runs, and one sample required re-analysis due to multiple endpoints in the titer assay. Deviations, including adjustment of acceptance ranges for positive controls, were not considered to impact study validity.

Out of 204 samples analyzed, 10 screened positive and 9 were confirmed as true positives, with antibody titers subsequently determined. The assay demonstrated high reliability, with a 90.5% batch acceptance rate and all controls meeting required criteria.

Neutralizing anti-GSK4057190 (dostarlimab) antibodies were assessed using a validated SPEAD ECL immunoassay. Nine ADA-positive, Day 1 pre-dose serum samples were analyzed in a single accepted run on 15-Apr-2025. Controls met acceptance criteria, the plate-specific cut point was acceptable, and all samples were below this threshold (NAb-negative). Method validation supports precision, specificity, stability, and drug/target tolerance.

6.3. Discussion

Pediatric pharmacokinetic data for niraparib and dostarlimab were evaluated relative to adult reference models to assess the appropriateness of pediatric dosing regimens.

Overall, method validation for determination of dostarlimab and niraparib were already presented and found to be acceptable in previous procedures. However, in accordance with the ICH M10 guideline, specificity is defined as: "*Ability of an analytical method to detect and differentiate the analyte from other substances, including its related substances (e.g., substances that are structurally similar to the analyte, metabolites, isomers, impurities, or concomitant medications)*." Given that study 213406 involves the concomitant administration of niraparib and dostarlimab, for future procedures it is highly recommended to study the specificity including all the related compounds to discard the cross-reactivity. Partial validations regarding extension of long-term stability for both substances overall comply with the ICH M10 guideline's specifications.

Sample analysis for niraparib and dostarlimab demonstrated acceptable performance and were compliant with the ICH M10 guideline. However, in the niraparib study, a fourth QC mid-high level was only incorporated in the final run. It is recommended per ICH M10 that at least four QC levels should be included in every analytical run, however, considering that the missing QC level corresponds to an intermediate concentration and that most QC samples met acceptance criteria, it is not deemed to impact the validity of the study. Additionally, a deviation regarding the number of ISR samples was fully justified and resolved, with no impact on method reproducibility. Overall, both methods were robust and suitable for their intended purpose.

For niraparib, pediatric exposures were compared with adult simulations under two dosing scenarios: 200 mg QD and a weight/platelet-adjusted 200/300 mg QD regimen, considering 2.5 h, 7 h, and 168 h post-dose. At 2.5 h, several pediatric cohorts (0, 1A, 1B, and osteosarcoma expansion) exhibited concentrations lower than adult simulations, suggesting delayed absorption, whereas cohorts 1 and neuroblastoma expansion cohort were comparable to adults under the adjusted 200/300 mg regimen. At 7 h and 168 h, cohorts 1B, cohort 1, and neuroblastoma expansion cohort demonstrated marked overexposure relative to adults, reaching up to 2–3 times simulated adult levels, while the

osteosarcoma expansion cohort remained within adult ranges. This inter-cohort variability highlights the need to consider cohort-specific dose adjustments.

In the SCOOP study, pediatric participants received dostarlimab 7.5 mg/kg Q3W (capped at 500 mg), and their observed concentrations were compared with the 95% prediction interval generated from 1,000 virtual adults simulated using the GARNET population PK model. Pediatric data were assessed alongside adult simulations for the 500-mg regimen at 1 h, 168 h, and 504 h post-dose. At 1 h, concentrations across pediatric cohorts (1A, 1B, osteosarcoma expansion, and neuroblastoma expansion) ranged from 124.7 to 186 ng/mL, while the adult simulated value was 159.6 ng/mL. At 168 h, pediatric values ranged from 55.6 to 91.8 ng/mL compared with 68.4 ng/mL in adults. At 504 h, concentrations in pediatric cohorts ranged from 35.1 to 45.7 ng/mL, and the corresponding adult simulation was 40.4 ng/mL. Across all three timepoints, pediatric concentration ranges included values close to those predicted in adults.

Immunogenicity conclusion

Validated assays used for ADAs and NAbs detection are found acceptable, demonstrating adequate specificity, sensitivity, precision, robustness, and stability. Sample analysis was performed in accordance with the validated method and is considered suitable for the detection and characterization of anti-drug antibodies (ADAs) as well as neutrilizing antibodies (NAbs).

Across all cohorts and dosing regimens, no treatment-emergent anti-drug antibodies (ADAs) were detected following administration of niraparib and dostarlimab. Among the 46 subjects with post-baseline ADA assessments, 100% remained ADA-negative throughout the evaluation period. Baseline ADA positivity was observed in 9 subjects (20%); however, all baseline-positive cases were classified as treatment-unaffected, with no evidence of treatment-induced or treatment-boosted responses.

Overall, these results indicate that single-dose administration of niraparib in combination with dostarlimab did not elicit an immunogenic response for the evaluated regimens.

7. Clinical Efficacy aspects

Study 213406 (SCOOP):

A phase 1, multicenter, open-label, dose escalation and cohort expansion study (two part trial) to evaluate pharmacokinetics, safety, activity and acceptability of niraparib in combination with dostarlimab in paediatric patients from 5 to less than 18 years of age with recurrent or refractory (R/R) solid tumors, excluding central nervous system (CNS) tumours in Part 1 and with R/R osteosarcoma and R/R neuroblastoma in Part 2. Part 1 was a dose-finding portion conducted in patients with solid tumors (excluding CNS tumours) that may have had a BRCAness mutational signature (osteosarcoma, neuroblastoma, adrenocortical carcinoma, Ewing sarcoma, or rhabdomyosarcoma) conferring sensitivity to PARP inhibition to establish the Recommended Phase 2 Dose (RP2D) of the combination of niraparib and dostarlimab in paediatric patients. Part 2 of the study evaluated efficacy and safety of the RP2D regimen in disease-specific expansion cohorts, osteosarcoma, and neuroblastoma.

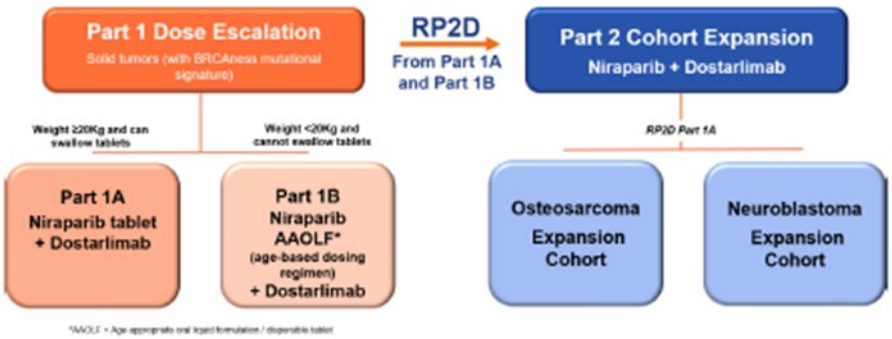
7.1. Methods – analysis of data submitted

Study design

Study 213406 (SCOOP) was a phase 1, multicentre, open-label, dose escalation (Part 1) and cohort expansion (Part 2) study.

The study design is outlined below.

Figure 4 Study design under protocol amendment 03 (or earlier)



Part 1A, a dose escalation to determine the RP2D of the combination of niraparib tablets and dostarlimab, included participants who were able to swallow the 100 mg niraparib tablets and who had a body weight of ≥20 kg. As of July 2023, enrollment on Part 1A was completed, and the RP2D for participants ≥20 kg and able to swallow the 100 mg niraparib tablet was determined to be niraparib 100 mg daily and dostarlimab 7.5 mg/kg (up to 500 mg) IV Q3W. This dose was subsequently evaluated for efficacy and safety in the Part 2 disease-specific expansion cohorts (2A osteosarcoma expansion cohort and 2B neuroblastoma expansion cohort).

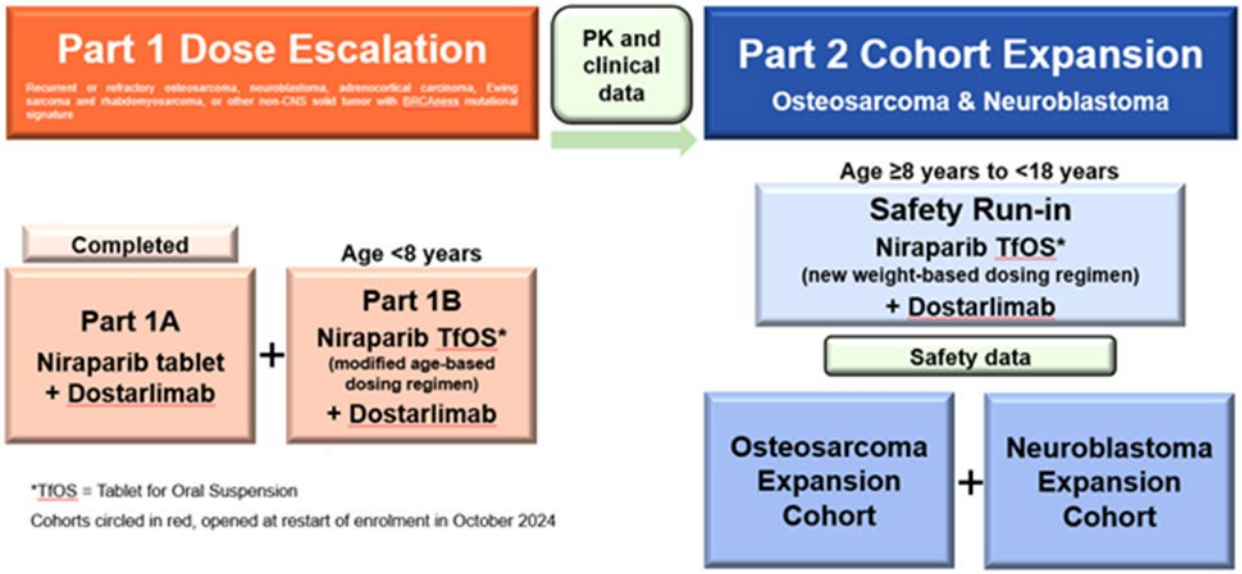
Part 1B, a dose escalation to determine the RP2D of the combination of niraparib age-appropriate oral liquid formulation (AAOLF) and dostarlimab, under protocol amendment 03 (or earlier), included patients who could not swallow the 100 mg niraparib tablets or who had a body weight of <20 kg. The dispersible niraparib tablet used in the study for Part 1B under protocol amendment 03 (and earlier) was referred to as age-appropriate oral liquid formulation (AAOLF).

Six events of Grade ≥3 thrombocytopenia reported in the Part 2 neuroblastoma expansion cohort and in Part 1B led to an enrollment pause in all cohorts of the study on 04 July 2023.

Following a comprehensive data review, enrollment reopened in October 2024 under protocol amendment 04 with modified niraparib dosing regimens (modified age-based dosing in patients <8 years and weight-based dosing in patients ≥8 years to <18 years) and a modified study design. At this time, the niraparib formulation was not changed; however, the name of the niraparib dispersible tablet was changed from AAOLF to tablet for oral suspension (TfOS). Niraparib was supplied as TfOS in both Part 1B and Part 2 of the study under protocol amendment 04.

Part 1B was planned as a dose escalation to determine the RP2D of the combination of age-based niraparib TfOS regimen and dostarlimab in participants <8 years old. The Part 2 Safety Run-in was intended to evaluate the safety and tolerability of the weight-based niraparib TfOS dosing regimen and dostarlimab in participants ≥8 years old prior to potential further enrollment into disease-specific expansion cohorts including paediatric patients ≥20 kg and able to swallow 100 mg niraparib tablets.

Figure 5 Study design under protocol amendments 04 and 05



The original protocol for this study was dated 12 May 2020. There was a total of 6 amendments. Below is a summary of key changes from each of the 6 amendments:

• **Amendment 01 (16 October 2020)** revised the protocol requirement for tumour assessments to be aligned with current standard of care and provided other clarifications and editorial changes. Additionally, minor changes to the time allowed for safety reporting were added to ensure consistency with GSK standard practices.

• **Amendment 02 (23 November 2020)** revised the protocol to include specific safety language noted during Health Authority review, and clarifications were made to inclusion and exclusion criteria.

• **Amendment 03 (20 July 2022)** revised the study protocol to update safety guidance, included a new appendix for the International Neuroblastoma Response Criteria (INRC), added a benefit risk section based on clinical studies of niraparib and dostarlimab, updated objectives and/or endpoints for secondary PK, immunogenicity, and exploratory analyses, updated eligibility criteria, added a statement about potential ad-hoc tumor sample collection for biomarker analyses in cases of specific clinical presentation, and increased clarity and/or removed discrepancies.

• **Amendment 04 (23 May 2024)** described changes in the niraparib dosing regimens based on emerging data and safety information and introduced the Part 2 Safety Run-in cohort. The name of the dispersible niraparib tablet was changed from AAOLF to TfOS. Administrative, editorial, and clarifications for study conduct were also included.

• **Amendment 04 GBR-1 (08 August 2024)** was a UK-specific amendment addressing agency feedback regarding exclusion criterion 15.

• **Amendment 05 (12 December 2024)** aligned Protocol Amendment 04 with all aspects of the UK-specific Protocol Amendment 04 GBR-1, resulting in a single global amendment. Additional changes included an update of the sponsor's legal registered address, administrative and editorial updates and clarifications for study conduct, as well as introducing the film-coated form of niraparib. Protocol Amendment 05 was not implemented prior to the study's early termination. The European Union Clinical Trial Regulation Protocol Amendment 05 substantial modification was withdrawn to allow for the submission of the study's early termination in the Clinical Trial Information System. The Medicines

and Healthcare Regulatory Authority regulatory review proceeded, and Protocol Amendment 05 received approval in the United Kingdom on 20 March 2025.

Study population /Sample size

Inclusion criteria

Part 1A and Part 1B:

1. Patients must have recurrent or refractory osteosarcoma, neuroblastoma, adrenocortical carcinoma, Ewing sarcoma, rhabdomyosarcoma, or any other solid tumour (excluding tumours of the CNS) and must not have been eligible for alternative curative treatment
2. Child or adolescent ≥6 months to <18 years old at the time of informed consent/assent. If a patient was enrolled under protocol amendment 05, the patient must have been ≥6 months to <8 years old at the time of informed consent/assent.
3. Patient with disease other than neuroblastoma had radiologically measurable disease at screening that could be tracked as RECIST v1.1 target lesion(s). Patient with neuroblastoma had measurable/evaluable target and/or non-target disease by International Neuroblastoma Response Criteria (INRC) at screening. Neuroblastoma patients with recurrent/relapsed bone metastasis that was iodine meta-iodobenzylguanidine, meta-iodobenzylguanidine (MIBG-positive) (or fluorodeoxyglucose, FDG positive, for MIBG-nonavid tumors) as only site of disease were eligible.

Part 2 Safety Run-in, and Part 2A and Part 2B Expansion Cohorts:

1. Patient had recurrent or refractory osteosarcoma or neuroblastoma and must not have been eligible for alternative curative treatment. Documentation of BRCAness mutational signature 3 was requested, but not required, for enrollment.
2. At screening, it was to be confirmed that an archival formalin-fixed and paraffin embedded (FFPE) tumour tissue sample of sufficient quality and quantity was available from the patient for use in retrospective exploratory biomarker analysis. Bone samples must have been decalcified using EDTA.

Exclusion criteria

Part 1A and Part 1B:

1. Patient had known hypersensitivity to dostarlimab or niraparib, their components, or their excipients.

2. Known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML).

3. Active autoimmune disease that required systemic treatment in the past 2 years. Replacement therapy was not considered a form of systemic treatment.

4. Know active CNS metastases, carcinomatous meningitis, or both.

5. Diagnosis of immunodeficiency or was receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment.

6. Any known Grade 3 or 4 anaemia, neutropenia, and/or thrombocytopenia that was related to the most recent prior anticancer treatment and that persisted >4 weeks (28 days).

7. Patient had not recovered (i.e., to Grade ≤1 or to baseline) from prior systemic anticancer therapy induced AEs.

8. Patient had toxicity related to prior immunotherapy that led to treatment discontinuation.

9. Patient had treatment with systemic anticancer therapy within 3 weeks or 5 half-lives, whichever was shorter, prior to first dose of study treatment; radiation therapy encompassing >20% of the bone marrow within 2 weeks prior to the first dose of study treatment; or any radiation therapy within 1 week prior to the first dose of study treatment.

Part 2 Safety Run-in, and Part 2A and Part 2B Expansion Cohorts:

1. Patient received prior therapy with an anti-PD 1, anti-PD-L1, anti-PD-L 2, anticytotoxic Tlymphocyte-associated antigen-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (exception of participants rolling over from Part 1 of the study: these participants were allowed to have received dostarlimab).
2. Patient had prior treatment with a known PARP inhibitor (exception of participants rolling over from Part 1 of the study: these participants were allowed to have received niraparib).

Treatments

Niraparib was administered orally in combination with dostarlimab administered via intravenous infusion once every 3 weeks (Q3W). Niraparib was supplied as dispersible tablets referred as age-appropriate oral liquid formulation (AAOLF) in Part 1B under protocol amendment 03 (and earlier) and as tablet for oral suspension (TfOS) in Part 1B and Part 2 of the study under protocol amendment 04. The name of the niraparib dispersible tablet was changed but the niraparib formulation was not changed.

Part 1A: up to 4 dose level cohorts were planned for Part 1A. Only 3 of the 4 cohorts were completed due to toxicity. RP2D was determined based on the 3 tested cohorts.

- Cohort 0: niraparib 100 mg daily dose (DL1) plus dostarlimab 3 mg/kg Q3W (maximum 500 mg)
- Cohort 1A: niraparib 100 mg daily dose (DL1) plus dostarlimab 7.5 mg/kg Q3W (maximum 500 mg)
- Cohort 1B: niraparib 200 mg daily dose (DL2) plus dostarlimab 3 mg/kg Q3W (maximum 500 mg)
- Cohort 2: niraparib 200 mg (DL2) plus dostarlimab 7.5 mg/kg Q3W (maximum 500 mg). No patients were enrolled into Part 1A: Cohort 2 as Part 1A: Cohort 1B was not deemed to be safe.

Part 1B: up to 3 dose level cohorts were planned for Part 1B. Patients were enrolled only in Part 1B: Cohort 1, with enrollment paused after 3 patients due to toxicity.

- Cohort 1: niraparib AAOLF (DL1) (dose based on popPK) and dostarlimab RP2D from Part 1A
- Cohort 2: niraparib AAOLF (DL2) (dose increase guided by PK) and dostarlimab RP2D from Part 1A
- Cohort -1: niraparib AAOLF (DL-1) (dose decrease guided by PK) and dostarlimab RP2D from Part 1A.

Once the RP2D of the combination of niraparib tablet and dostarlimab was established in Part 1A, Part 2 (under protocol amendment 03) was opened to accrual for participants who were able to swallow the 100 mg niraparib tablets and had a body weight of ≥20 kg. All patients in Part 2 received the RP2D established in Part 1A: 100 mg niraparib plus 7.5 mg/kg dostarlimab Q3W (maximum 500 mg).

Under protocol amendment 03, the starting dose level for dostarlimab in Part 1B was the RP2D as determined from Part 1A (7.5 mg/kg Q3W; maximum 500 mg), and the starting dose level for niraparib AAOLF was determined by PK evaluation using all available concentration data from Part 1A and modelling and simulation approaches. Up to 3 dose level cohorts were anticipated.

Enrollment in original Part 1B: Cohort 1, Part 2A, and Part 2B was paused due to AEs of Grade 3 and Grade 4 thrombocytopenia reported in patients in Part 1B and Part 2B (neuroblastoma expansion). Dose escalation in the original Part 1B did not advance past Cohort 1.

Under protocol amendment 04, enrollment was opened in the new Part 2 Safety Run-in cohort for participants ≥8 years old to <18 years of age using the updated niraparib weight-based dosing regimen in combination with 7.5 mg/kg dostarlimab Q3W (maximum 500 mg). Enrollment in the Part 2 Expansion Cohorts was to start following determination of the safety of the new weight-based niraparib TfOS dosing regimen in combination with dostarlimab in the Part 2 Safety Run-in cohort.

Also under protocol amendment 04, enrollment into new Part 1B: Cohort 1 was opened using a modified age-based niraparib dosing regimen in combination with 7.5 mg/kg dostarlimab Q3W (maximum 500 mg). The goal of Part 1B dose escalation was to determine the RP2D for the age-based niraparib dosing regimen in combination with dostarlimab for participants ≥6 months to <8 years. Once the RP2D of this niraparib plus dostarlimab combination had been determined for this younger age group, enrolment into Part 2 could have proceeded for these younger participants.

Table 6 Number of participants in the safety population, and niraparib and dostarlimab dose level by cohort

Cohort	N	Niraparib dose (mg QD)	Dostarlimab dose
Part 1A Cohort 0	11	100 mg	3 mg/kg Q3W
Part 1A Cohort 1A	7	100 mg	7.5 mg/kg Q3W
Part 1A Cohort 1B	5	200 mg	3 mg/kg Q3W
Part 1B Cohort 1	3	Age-based dosing	7.5 mg/kg Q3W
Part 2A Neuroblastoma expansion cohort	7	100 mg	7.5 mg/kg Q3W
Part 2B Osteosarcoma expansion cohort	11	100 mg	7.5 mg/kg Q3W
Part 2 Safety Run-in	3	Weight-based dosing	7.5 mg/kg Q3W

The safety population included all participants who received at least one dose of either niraparib or dostarlimab.

Objectives

The primary objective of Study 213406 was to establish the recommended phase 2 dose (RP2D) and evaluate the safety, activity and tolerability, of the combination of niraparib and dostarlimab in paediatric patients with recurrent or refractory solid tumours.

Secondary objectives included:

- Characterization of the PK of the combination of niraparib and dostarlimab,
- Assessment of the immunogenicity of dostarlimab,
- Assessment of acceptability and palatability of niraparib tablets and tablets for oral suspension (TfOS),
- Evaluation of additional measures of anticancer activity including ORR, DOR, DCR and PFS, in paediatric patients.

Exploratory objectives include assessment of biomarkers related to PARP inhibition and/or anti-PD-1 therapy and correlation with clinical outcome in paediatric patients.

Outcomes/endpoints

The primary efficacy endpoints were incidence of dose limiting toxicity (DLTs) by study part and cohort for the DLT evaluable population (Part 1A; Part 1B; Part 2 Safety Run-in), progression-free survival (PFS) at 6 months (PFS6) in Part 2A (Osteosarcoma Expansion Cohort), and objective response rate (ORR) in Part 2B (Neuroblastoma Expansion Cohort).

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. PFS6 was evaluated as a binary endpoint in patients from Part 2A in combination with patients from Part 1A of the study who satisfied the inclusion and exclusion criteria for Part 2 of the study, satisfied the mITT population definition, and were treated at the same dose as that used in Part 2A.

ORR is 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 International Neuroblastoma Response Criteria (INRC). Primary analysis of ORR in Part 2B was conducted after participants had at least 6 months of follow-up, had documented disease progression, had withdrawn from the study, or had died. Participants from Part 1 of the study who satisfied the inclusion and exclusion criteria for Part 2 of the study, satisfied the mITT population definition, and were treated at the same dose as that used in Part 2B were included in the Part 2B efficacy analysis.

Key secondary endpoints were ORR, duration of response (DOR), disease control rate (DCR).

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 patients with neuroblastoma or RECIST v1.1 for patients with osteosarcoma based on Investigator assessment or death (whichever occurs first).

DCR is defined as the proportion of patients who have achieved a BOR of confirmed CR, confirmed PR, or stable disease by INRC for patients with neuroblastoma or RECIST v1.1 for patients with osteosarcoma based on Investigator assessment.

Statistical Methods

All analyses included summary statistics, including number of participants and percentage for categorical variables, and number of participants, mean, standard deviation, median, minimum, and maximum for continuous variables. Two-sided exact 95% CIs based on the Clopper-Pearson method were provided where appropriate (Clopper, 1934). Time-to-event analyses was performed using Kaplan-Meier methods.

For Part 1, no formal interim analysis was planned. However, a review of safety data and available preliminary PK data were conducted by the Sponsor and Investigators following completion of the DLT observation periods in Part 1A, Part 1B, and completion of the Part 2 Safety Run-in. Determination of the RP2D from Part 1A was based on review of safety and available PK data. An mTPI-2 dose escalation design was used for the evaluation of safety at each dose level.

The incidence of DLTs (primary endpoint) was summarized by study part and cohort for the DLT-evaluable population.

The number and proportion of participants with an objective response (secondary efficacy endpoint) was tabulated by dose cohort and overall. ORR was calculated, along with its estimated 2-sided 95% CI. Among the participants with a confirmed response, a time-to-event analysis of DOR was performed using Kaplan-Meier method, including quartile estimates and two-sided 95% CI.

<u>Sample size determination</u>

The sample size of the study (approximately 56 patients in total) was not based on formal statistical hypotheses, but is estimated based on an mTPI-2 dose escalation design for Part 1 including approximately 7 cohorts (4 cohorts planned in Part 1A under Protocol amendment 03 and 3 cohorts planned in Part 1B under protocol amendment 05 [8 participants per each of the 7 cohorts]). Up to 5 additional patients may be enrolled to further evaluate the youngest participant group(s) if not represented.

Analysis population/Analysis Sets

The primary analysis set for the efficacy endpoints was the mITT Population.

Additional safety data were summarized for the safety population for all parts of the study. Safety parameters were performed in all safety population. Descriptive statistics of safety are presented using NCI CTCAE version 5. No formal hypothesis-testing analysis of AE incidence rates was performed. AEs were classified according to MedDRA version 20.0 or later. All AEs occurring during the study were included in by participant data listings and tabulated by MedDRA system organ class and preferred term. TEAE was defined as any AE with onset after the first administration of study treatment, throughout the Treatment Period, until 30 days after cessation of study treatment (90 days for SAEs) (or until the start of new anticancer treatment whichever occurs earlier), or any event that was present at baseline but worsened in intensity or was subsequently considered study treatment-related by the Investigator through the end of the study.

Table 7 Analysis Set

Participant Analysis Set	Description
Safety	The Safety Population is defined as all participants who receive at least 1 dose of either niraparib or dostarlimab.
Intent-to-Treat (ITT)	The ITT Population includes all participants who receive any study medication and have measurable baseline tumour assessment and/or, for neuroblastoma participants, MIBG-positive disease (or FDG-positive disease, for MIBG-nonavid tumours) at baseline.
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-positive disease, for MIBG-nonavid-tumours) at baseline, and have at least 1 postbaseline tumour assessment.
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.
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 infusions of dostarlimab) or experience a DLT.
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.
Immunogenicity (ADA) Population	The ADA Population includes all participants who receive at least 1 dose of dostarlimab and who have at least 1 ADA sample with a result.

Abbreviations: ADA=antidrug antibody; DLT=dose limiting toxicity; ITT=Intent-to-Treat; mITT=modified Intent-to-Treat; PK=pharmacokinetic.

7.2. Results

Participant flow

Table 8 Summary of subject Tstatus and subject disposition for the study conclusion record (screened population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2:Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5 mg/kg N=3	Total N=50
Subject Status[1]								
Ongoing	0	0	0	0	0	0	0	0
Completed	0	0	0	0	0	0	0	0
Discontinued	11 (100.0)	7 (100.0)	5 (100.0)	3 (100.0)	11 (100.0)	7 (100.0)	3 (100.0)	47 (94.0)
Primary Reason[2] for Study Discontinuation								
Adverse event	0	0	0	0	0	0	0	0
Death	7 (63.6)	3 (42.9)	3 (60.0)	3 (100.0)	1 (9.1)	2 (28.6)	1 (33.3)	20 (40.0)
Lack of efficacy	0	0	0	0	0	0	0	0
Lost to follow-up	0	0	0	0	1 (9.1)	0	0	1 (2.0)
Physician decision	0	0	0	0	5 (45.5)	0	0	5 (10.0)
Progressive disease	0	0	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0	0	0
Site terminated by sponsor	0	0	0	0	0	0	0	0
Sponsor terminated study treatment	0	0	0	0	0	0	0	0
Study terminated by sponsor	1 (9.1)	0	0	0	0	0	1 (33.3)	2 (4.0)
Subject reached protocol-defined stopping criteria	3 (27.3)	4 (57.1)	2 (40.0)	0	4 (36.4)	4 (57.1)	1 (33.3)	18 (36.0)
Withdrawal by subject	0	0	0	0	0	1 (14.3)	0	1 (2.0)
Other	0	0	0	0	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation; TfOS=Tablet for Oral Suspension.
[1] 'Discontinued' means permanent discontinuation of a study.
[2] Subjects may have only one primary reason

Overall, a total of 50 patients were screened, 47 were treated in this study.

Under Protocol Amendment 03, a total of 23 patients were treated in Part 1A. In addition, 3 patients were treated in Part 1B and 18 patients in Part 2 (11 in Part 2A and 7 in Part 2B) prior to the pause of enrollment due to AEs of Grade ≥3 thrombocytopenia. For the Part 2 Cohort Expansion, a total of 18 patients, 11 in Part 2A (osteosarcoma cohort) and 7 in Part 2B (neuroblastoma cohort), were treated prior to the pause of enrollment due to AEs of Grade ≥3 thrombocytopenia.

Under Protocol Amendment 04, 3 patients were treated in Part 2 Safety Run-in. No patients were treated in Part 1B.

Of the 50 patients in the screened population, no patients were ongoing in Part 1 or Part 2 at the time of data base lock (DBL), and no participants had completed the study, all participants were discontinued from the study overall.

Recruitment

Subjects were enrolled at 26 sites in 4 countries: Czech Republic, France, Spain, and the UK. No participants were screened in 2 countries: Hungary and Germany.

Baseline data

The demographic characteristics and disease characteristics of the overall population are summarized in the below table.

The mean (SD) age of participants in the study was 12.9 (3.50) years and ranged from 5 to <18 years of age. Patients in cohorts diagnosed with neuroblastoma tended to be younger and were of lower body weight than other participants.

Table 9 Summary of Demographic Characteristics and Disease Characteristics at Initial Diagnosis (Screened Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3	Total N=50
Sex								
n	11	7	5	3	11	7	3	50
Female	1 (9)	5 (71)	3 (60)	3 (100)	5 (45)	3 (43)	2 (67)	24 (48)
Male	10 (91)	2 (29)	2 (40)	0	6 (55)	4 (57)	1 (33)	26 (52)
Age (YEARS)								
n	11	7	5	3	11	7	3	50
Mean (SD)	13.9 (2.84)	13.7 (3.99)	13.0 (3.81)	6.0 (1.0)	14.3 (2.45)	10.1 (2.97)	14.7 (1.53)	12.9 (3.50)
Median	15.0	15.0	14.0	6.0	14.0	10.0	15.0	14.0
Min	9	9	9	5	10	7	13	5
Max	17	18	17	7	17	15	16	18
Weight (kg)								
n	11	7	5	3	11	7	3	47
Mean (SD)	47.6 (14.78)	47.1 (23.54)	64.5 (22.93)	18.6 (1.70)	55.8 (17.01)	36.1 (12.63)	50.2 (24.45)	47.9 (19.95)
Median	51.0	38.2	65.0	17.7	59.2	39.0	44.0	45.2
Min	23	20	41	18	25	21	30	18
Max	68	92	97	21	83	51	77	97
Karnofsky Scale								
n	2	3	1	0	3	0	0	9
Mean (SD)	80.0 (14.14)	96.7 (5.77)	100.0 (NA)	NA	96.7 (5.77)	NA	NA	93.3 (10.00)
Median	80.0	100.0	100.0	NA	100.0	NA	NA	100.0
Min	70	90	100	NA	90	NA	NA	70
Max	90	100	100	NA	100	NA	NA	100
Lansky Scale								
n	9	4	4	3	8	7	3	38
Mean (SD)	93.3 (8.66)	92.5 (9.57)	92.5 (5.00)	96.7 (5.77)	85.0 (11.95)	94.3 (11.34)	90.0 (17.32)	91.6 (10.27)
Median	100.0	95.0	90.0	100.0	85.0	100.0	100.0	95.0
Min	80	80	90	90	70	70	70	70
Max	100	100	100	100	100	100	100	100
Tumor Type								
Osteosarcoma	5 (45)	1 (14)	3 (60)	0	11 (100)	0	3 (100)	NA
Neuroblastoma	0	3 (43)	0	3 (100)	0	7 (100)	0	NA
Adrenocortical carcinoma	0	1 (14)	0	0	0	0	0	NA
Ewing sarcoma	5 (45)	1 (14)	1 (20)	0	0	0	0	NA
Rhabdomyosarcoma	1 (9)	1 (14)	1 (20)	0	0	0	0	NA
Stage of Tumor at Screening								
Stage IV	10 (91)	7 (100)	5 (100)	3 (100)	7 (64)	7 (100)	3 (100)	NA
Stage IVA	0	0	0	0	2 (18)	0	0	NA
Stage IVB	1 (9)	0	0	0	1 (9)	0	0	NA
Missing	0	0	0	0	1 (9)	0	0	NA
Time since Initial Diagnosis (Months)								
n	11	7	5	3	11	7	3	NA
Mean (SD)	33.93 (23.319)	50.20 (50.094)	24.80 (10.948)	39.49 (8.265)	23.16 (14.332)	55.11 (36.823)	19.58 (9.181)	NA
Median	24.48	41.43	27.66	41.89	22.11	58.87	22.01	NA
Q1	17.22	12.58	17.05	30.29	11.73	19.84	9.43	NA
Q3	62.06	72.90	31.67	46.29	30.49	71.39	27.30	NA
Min	5.5	6.6	10.3	30.3	6.2	17.5	9.4	NA
Max	72.8	148.8	37.3	46.3	55.7	124.0	27.3	NA
Line of Anticancer Therapy								
1	1 (9)	1 (14)	0	0	1 (9)	0	0	NA
2	6 (55)	1 (14)	3 (60)	0	8 (73)	1 (14)	3 (100)	NA
3	2 (18)	2 (29)	1 (20)	0	2 (18)	2 (29)	0	NA

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3	Total N=50
4	1 (9)	0	1 (20)	2 (67)	0	2 (29)	0	NA
≥5	1 (9)	3 (43)	0	1 (33)	0	2 (29)	0	NA
Best Response for Last Anticancer Therapy								
Complete response	4 (36)	4 (57)	2 (40)	2(67)	4 (36)	3 (43)	0	NA
Very good partial response	1 (9)	0	0	0	0	0	0	NA
Partial response	4 (36)	1 (14)	2 (40)	1 (33)	0	3 (43)	2 (67)	NA
Minimal response	0	0	0	0	0	0	1 (33)	NA
Stable disease	2 (18)	1 (14)	1 (20)	0	1 (9)	1 (14)	0	NA
Progressive disease	0	1 (14)	0	0	6 (55)	0	0	NA

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation; Max=Maximum; Min=Minimum; NA=not applicable; Q1=first quarter; Q3=third quarter; SD=standard deviation; TfOS=Tablet for Oral Suspension.

[1] Participant in Part 1A Cohort 1A age 18 at consent: participant was <18 years of age at consent and hence met all eligibility criteria. Reason: the clinical database standardly records first of the month for the day of birth as the real day of birth is not recorded for subject confidentiality; therefore this led to discrepancy between the real and the recorded date of birth and age at consent.

Number analysed

There were three patients in the screened population who were not assigned to any cohort. The Intention-to-Treat population was used for the analysis of Part 1 and modified Intention-to-Treat population was used in the analysis of the efficacy endpoints in Part 2.

Table 10 Study populations

Population, n (%)	Part 1A (N=23)	Part 1B (N=3)	Part 2A (N=11)	Part 2B (N=7)	Part 2 Safety Run-In (N=3)
Screened[a]	23	3	11	7	3
Safety	23	3	11	7	3
Intent-to-Treat	22	3	NA	NA	NA
Modified Intent-to-Treat	NA	NA	9[b]	8[b]	3
DLT-evaluable	16	2	NA	NA	3
Pharmacokinetic	23	3	11	7	3
Immunogenicity	23	3	11	7	3

Abbreviations: DLT=dose-limiting toxicity; NA=not applicable; SAP=Statistical Analysis Plan.
Note: Subjects are included in the Safety Population if they had taken at least one dose of study treatment.
Note: For key definitions of each population, see the SAP, Section 3.
Source: Table 1.1, Table 1.4, Table 2.1, Table 2.4, Table 3.3, Table 4.1, Table 5.1

a. Three participants in the Screened population were not assigned to any cohort.
b. Those Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfied the mITT population definition, and were treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis.

Efficacy results

Primary endpoints:

- Part 2A (Osteosarcoma Expansion Cohort)

Progression-free survival at 6 months (PFS6) was evaluated as a binary endpoint in participants from Part 2A in combination with participants from Part 1A of the study who satisfied the inclusion and exclusion criteria for Part 2 of the study, satisfied the mITT population definition, and were treated at the same dose as that used in Part 2A.

Of the 9 patients included in the mITT population, a response was not reported for any participant. PFS6 in the mITT analysis set was 0 with 95% CI (0.0%, 33.6%), with all participants reporting progressive disease or death before 6 months.

The interim analysis success criterion for the primary efficacy endpoint of PFS6 was not achieved.

Table 11 Summary of Progression-Free Survival at 6 months (PFS6) (mITT Population)

	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg N=9
PFS6	
Progressive disease or death	9 (100%)
No progressive disease or death	0

	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg N=9
Progression-Free Survival rate at 6 months (PFS6)	
Rate	0
95% Confidence Interval	(0.0%, 33.6%)

Abbreviations: mITT=modified intent-to-treat; PFS6=progression-free survival rate at 6 months.
Note: Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfied the mITT Population definition, and were treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis: 1 participant from Part 1A Cohort 1A was analyzed in Osteosarcoma cohort.

A sensitivity analysis was performed. PFS was analyzed using non-parametric Kaplan-Meier method on the ITT analysis set. Median PFS in months was 1.2 (95% CI 0.7, 2.1).

Table 12 Summary of Kaplan-Meier Estimates of Progression-Free Survival

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Population: Modified Intent-to-treat

Table 2.4
Summary of Kaplan-Meier Estimates of Progression-Free Survival

	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=9)	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=8)
Number of Subjects		
Progressed or died (event)	9 (100%)	8 (100%)
Censored, Follow-up ended	0	0
Censored, Follow-up ongoing	0	0
Event Summary		
Disease progression	9 (100%)	7 (88%)
Death	0	1 (13%)
Estimates for Time Variable (Months) [1]		
1st Quartile	1.0	1.4
95% Confidence Interval	(0.7, 1.2)	(0.5, 3.6)
Median	1.2	2.9
95% Confidence Interval	(0.7, 2.1)	(0.5, 10.2)
3rd Quartile	2.0	7.8
95% Confidence Interval	(1.2, NE)	(1.9, NE)

[1] Quartiles estimates are based on product-limit method. Confidence Intervals estimated using the Brookmeyer Crowley method.
Note: Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfy the mITT Population definition, and are treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis: 1 participant from Part 1A Cohort 1A is analyzed in Osteosarcoma cohort and 2 participants from Part 1A Cohort 1A are analyzed in Neuroblastoma cohort.
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- Part 2B (Neuroblastoma Expansion Cohort)

Primary analysis of ORR in Part 2B was conducted after participants had at least 6 months of follow-up, had documented disease progression, had withdrawn from the study, or had died. Participants from Part 1 of the study who satisfied the inclusion and exclusion criteria for Part 2 of the study, satisfied the mITT population definition, and were treated at the same dose as that used in Part 2B were included in the Part 2B efficacy analysis.

Of the 8 patients included in the mITT analysis set, a response was not reported for any participant (ORR of 0%, 95% CI [0.0%, 36.9%]). Due to the low sample size for the analysis, a conclusion could not be made on whether the interim analysis success criteria were achieved for the endpoint, however, no responders were observed in the analyzed patients.

No sensitivity analyses were performed.

Table 13 Summary of Confirmed Investigator Assessed Best Response (INRC) (mITT Population)

	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg N=8
Best Response (BoR)	
Complete Response (CR)	0
Partial Response (PR)	0
Stable Disease (SD)	4 (50%)
Progressive Disease (PD)	4 (50%)
Not Evaluable (NE)	0
Objective Response Rate (ORR)	
[CR+PR]	0
95% Confidence Interval	(0.0%, 36.9%)
Disease Control Rate (DCR)	
[CR+PR+SD]	3 (38%)
95% Confidence Interval	(8.5%, 75.5%)

Abbreviations: BoR= best response rate; DCR=disease control rate; mITT=modified intent-to-treat INRC=International Neuroblastoma Response Criteria; SD=stable disease.

Note: Confidence Intervals estimated using the Clopper-Pearson method.

Note: To be assigned a status of SD for BoR, follow-up disease assessment must have met SD criteria at a minimum interval of 8 weeks (56 days) from baseline. To be assigned a status of SD for DCR, follow-up disease assessment must have met SD criteria at a minimum interval of 17 weeks (119 days) from baseline.

Note: Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfied the mITT Population definition, and were treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis: 2 participants from Part 1A Cohort 1A were analyzed in Neuroblastoma cohort.

Note: Minor Response is assigned as Stable Disease for the purpose of BoR evaluation.

Secondary endpoints:

- Part 1: One participant out of 11 (ORR of 9% [95% CI 0.2%, 41.3%]) in Part 1A Cohort 0 had a BoR of CR. Duration of this response was 37.29 months. The ORR was 0% (95% CI 0.0%, 45.9%) in Part 1A Cohort 1A, 0% (95% CI 0.0%, 52.2%) in Part 1A Cohort 1B, and 0% (95% CI 0.0%, 70.8%) in Part 1B Cohort 1.
- Part 2A: No participants in Part 2A reported a response (ORR of 0% [95% CI 0.0%, 33.6%] and DCR of 0% [95% CI 0.0%, 33.6%]) and median PFS was 1.2 months (95% CI 0.7, 2.1).
- Part 2B: No patients in Part 2B reported a response (ORR of 0% [95% CI 0.0%, 33.6%]). Three participants reported DCR (38% [95% CI 8.5%, 75.5%]) and median PFS was 2.9 months (95% CI 0.5, 10.2).

Table 13 Summary of Confirmed Investigator Assessed Best Response (RECIST 1.1 or INRC)

Protocol: 213406 Page 1 of 1
Population: Intent-To-Treat

Table 2.1
Summary of Confirmed Investigator Assessed Best Response (RECIST 1.1 or INRC)

	Part 1A: Cohort 0 Niraparib Tablet 100mg/ Dostarlimab 3mg/kg (N=11)	Part 1A: Cohort 1A Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=6)	Part 1A: Cohort 1B Niraparib Tablet 200mg/ Dostarlimab 3mg/kg (N=5)	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ Dostarlimab 7.5mg/kg (N=3)
Best Response (BoR)				
Complete Response (CR)	1 (9%)	0	0	0
Partial Response (PR)	0	0	0	0
Stable Disease (SD)	0	1 (17%)	0	0
Progressive Disease (PD)	6 (55%)	5 (83%)	4 (80%)	2 (67%)
Not Evaluable (NE)	4 (36%)	0	1 (20%)	1 (33%)
Objective Response Rate (ORR)				
[CR+PR]	1 (9%)	0	0	0
95% Confidence Interval	(0.2%, 41.3%)	(0.0%, 45.9%)	(0.0%, 52.2%)	(0.0%, 70.8%)
Disease Control Rate (DCR)				
[CR+PR+SD]	1 (9%)	0	0	0
95% Confidence Interval	(0.2%, 41.3%)	(0.0%, 45.9%)	(0.0%, 52.2%)	(0.0%, 70.8%)

Abbreviations: AAOLF = Age-appropriate Oral Liquid Formulation, INRC = International Neuroblastoma Response Criteria, RECIST = Response Evaluation Criteria in Solid Tumors.
Note: Confidence Intervals estimated using the Clopper-Pearson method.
Note: To be assigned a status of SD for BoR, follow-up disease assessment must have met SD criteria at a minimum interval of 8 weeks (56 days) from baseline. To be assigned a status of SD for DCR, follow-up disease assessment must have met SD criteria at a minimum interval of 17 weeks (119 days) from baseline.
Note: INRC have been used to estimate responses for Neuroblastoma subjects & RECIST 1.1 for other subjects.
Note: Minor Response is assigned as Stable Disease for the purpose of BoR evaluation.
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Table 14 Summary of Confirmed Investigator Assessed Best Response (RECIST 1.1)

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Population: Modified Intent-to-treat

Table 2.2
Summary of Confirmed Investigator Assessed Best Response (RECIST 1.1)

	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=9)
Best Response (BoR)	
Complete Response (CR)	0
Partial Response (PR)	0
Stable Disease (SD)	1 (11%)
Progressive Disease (PD)	8 (89%)
Not Evaluable (NE)	0
Objective Response Rate (ORR)	
[CR+PR]	0
95% Confidence Interval	(0.0%, 33.6%)
Disease Control Rate (DCR)	
[CR+PR+SD]	0
95% Confidence Interval	(0.0%, 33.6%)

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors.
Note: Confidence Intervals estimated using the Clopper-Pearson method.
Note: To be assigned a status of SD for BoR, follow-up disease assessment must have met SD criteria at a minimum interval of 8 weeks (56 days) from baseline. To be assigned a status of SD for DCR, follow-up disease assessment must have met SD criteria at a minimum interval of 17 weeks (119 days) from baseline.
Note: Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfy the mITT Population definition, and are treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis: 1 participant from Part 1A Cohort 1A is analyzed in Osteosarcoma cohort.
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Table 15 Summary of Investigator Assessed Best Response (INRC)

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Population: Modified Intent-to-treat

Table 2.3
Summary of Investigator Assessed Best Response (INRC)

	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ Dostarlimab 7.5mg/kg (N=8)
Best Response (BoR)	
Complete Response (CR)	0
Partial Response (PR)	0
Stable Disease (SD)	4 (50%)
Progressive Disease (PD)	4 (50%)
Not Evaluable (NE)	0
Objective Response Rate (ORR)	
[CR+PR]	0
95% Confidence Interval	(0.0%, 36.9%)
Disease Control Rate (DCR)	
[CR+PR+SD]	3 (38%)
95% Confidence Interval	(8.5%, 75.5%)

Abbreviations: INRC = International Neuroblastoma Response Criteria.
Note: Confidence Intervals estimated using the Clopper-Pearson method.
Note: To be assigned a status of SD for BoR, follow-up disease assessment must have met SD criteria at a minimum interval of 8 weeks (56 days) from baseline. To be assigned a status of SD for DCR, follow-up disease assessment must have met SD criteria at a minimum interval of 17 weeks (119 days) from baseline.
Note: Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2, satisfy the mITT Population definition, and are treated at the dose used in Part 2 Cohort Expansion were included in the Part 2 efficacy analysis: 2 participants from Part 1A Cohort 1A are analyzed in Neuroblastoma cohort.
Note: Minor Response is assigned as Stable Disease for the purpose of BoR evaluation.
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7.3. Discussion

See "Discussion on clinical efficacy and safety" below.

8. Clinical Safety aspects

8.1. Safety results

The data for the clinical safety of niraparib in combination with dostarlimab in paediatric patients from 5 years of age to less than 18 years of age with R/R solid tumours (excluding central nervous system tumours) in Part 1A and 1B and with R/R osteosarcoma and R/R neuroblastoma in Part 2, are provided from the SCOOP study. Database lock (DBL) was 09 June 2025.

The SCOOP study was initiated in October 2020. In July 2023, the enrolment paused in all study cohorts due to Grade 3 and 4 thrombocytopenia observed in patients. In October 2024, enrolment reopened with modified niraparib dosing regimens and additional risk mitigation measures including a safety run-in in Part 2. In March 2025, the study was closed for further enrolment due to observation of toxicity in conjunction with insufficient efficacy and was permanently terminated on 23 April 2025.

The safety assessments included the monitoring of AEs, clinical laboratory tests, vital signs, and ECGs. Assessments of safety (incidence of DLTs and Grade≥3 thrombocytopenia [Part 2 safety run-in only]) were included as primary objectives in Part 1 and the Part 2 Safety Run-in.

The safety population included all participants who received at least one dose of either niraparib or dostarlimab.

8.2. Exposure

The median duration of exposure for niraparib was 2.04 months or fewer in any part or cohort (Table 16). The median overall dostarlimab exposure was also approximately 2 months or fewer regardless of part or cohort (Table 17).

The median number of 21-day cycles of niraparib initiated was 3 or fewer in all study parts and cohorts (Table 16). The median number of Q3W dostarlimab cycles initiated was also 3 or fewer in all parts and cohorts (Table 17).

Table 16 Summary of exposure to niraparib (safety population)

n (%)		Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose) / dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2:Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Number of cycles initiated	n	11	7	5	3	11	7	3
	Mean	6.4	4.7	1.8	1.3	2.9	6.7	2.3
	SD	14.16	5.91	1.10	0.58	2.02	7.80	0.58
	Median	2.0	3.0	1.0	1.0	2.0	1.0	2.0
	Min.	1	1	1	1	1	1	2
	Max.	49	18	3	2	8	18	3
	4 cycles	0	0	0	0	0	0	0
	<4 cycles	10 (91)	6 (86)	5 (100)	3 (100)	9 (82)	4 (57)	3 (100)
	>4 cycles	1 (9)	1 (14)	0	0	2 (18)	3 (43)	0
Overall treatment exposure (months)	n	11	7	5	3	11	7	3
	Mean	4.32	3.28	1.18	1.19	1.85	4.71	1.72
	SD	9.869	4.033	0.703	0.408	1.444	5.182	0.363
	Median	1.41	2.04	0.99	1.41	1.35	1.94	1.68
	Min	0.4	0.7	0.4	0.7	0.2	0.5	1.4
	Max	34.0	12.4	2.1	1.4	5.5	12.0	2.1
Actual treatment exposure (months)	n	11	7	5	3	11	7	3
	Mean	4.08	3.05	0.93	0.65	1.71	4.38	1.43
	SD	9.529	4.145	0.579	0.198	1.493	5.300	0.522
	Median	1.38	1.87	0.72	0.62	1.35	0.82	1.15
	Min	0.2	0.7	0.4	0.5	0.1	0.3	1.1
	Max	32.8	12.4	1.5	0.9	5.3	11.8	2.0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation; Min=minimum; Max=maximum; SD=standard deviation; TfOS=Tablet for Oral Suspension.

Note: Number of cycles initiated was calculated as maximum cycle number in which subject received Niraparib. Overall treatment exposure was calculated as (date of last dose - date of 1st dose +1)/30.4375. If the date of last dose is missing, last dose date is imputed with min of (last cycle date +20, End of Treatment date). Actual treatment exposure was calculated as overall treatment exposure minus duration of interruptions.

Table 17 Summary of exposure to dostarlimab (safety population)

n (%)		Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose) / dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5 mg/kg N=3
Number of cycles initiated	n	11	7	5	3	11	7	3
	Mean	6.4	4.7	1.8	1.7	2.9	7.0	2.3
	SD	14.16	5.91	1.10	0.58	2.02	7.59	0.58
	Median	2.0	3.0	1.0	2.0	2.0	3.0	2.0
	Min.	1	1	1	1	1	1	2
	Max.	49	18	3	2	8	18	3
	4 cycles	0	0	0	0	0	0	0
	<4 cycles	10 (91)	6 (86)	5 (100)	3 (100)	9 (82)	4 (57)	3 (100)
	>4 cycles	1 (9)	1 (14)	0	0	2 (18)	3 (43)	0
Overall treatment exposure (months)	n	11	7	5	3	11	7	3
	Mean	4.17	3.12	1.03	0.78	1.76	4.51	1.51
	SD	9.791	4.102	0.748	0.348	1.515	5.289	0.466
	Median	1.38	1.91	0.69	0.72	1.35	1.45	1.35
	Min	0.2	0.7	0.4	0.5	0.1	0.3	1.1
	Max	33.6	12.4	2.0	1.1	5.5	12.0	2.0
Actual treatment exposure (months)	n	11	7	5	3	11	7	3
	Mean	4.17	3.12	1.03	0.78	1.76	4.51	1.51
	SD	9.791	4.102	0.748	0.348	1.515	5.289	0.466
	Median	1.38	1.91	0.69	0.72	1.35	1.45	1.35
	Min	0.2	0.7	0.4	0.5	0.1	0.3	1.1
	Max	33.6	12.4	2.0	1.1	5.5	12.0	2.0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation; Min=minimum; Max=maximum; SD=standard deviation; TfOS=Tablet for Oral Suspension.
Note: Number of cycles initiated was calculated as maximum cycle number in which subject received dostarlimab. Overall treatment exposure was calculated as (max(date of last dose, end of treatment date) - date of 1st dose +21)/30.4375. Actual treatment exposure was calculated as overall treatment exposure minus duration of interruptions.

8.3. Adverse events

Dose-limiting toxicities (DLTs)

DLTs were experienced by 7 patients in total, 4 out of 16 DLT-evaluable patients in Part 1A (25%), 2 out of 2 DLT-evaluable patients (100%) in original Part 1B, and 1 of 3 DLT-evaluable patients (33%) in Part 2 Safety Run-in:

Part 1A, Cohort 0: a patient with osteosarcoma received treatment with niraparib 100 mg oral once daily and dostarlimab 3mg/kg dose IV Q3W, experienced an AE of Grade 3 anemia requiring transfusion, considered related to niraparib.

Part 1A, Cohort 1A: a patient with neuroblastoma, received treatment with niraparib 100 mg oral once daily and dostarlimab 7.5 mg/kg dose IV Q3W, experienced SAEs of Grade 3 nausea and Grade 3 vomiting considered related to niraparib, and an AE of Grade 3 anorexia considered related to niraparib and dostarlimab; the patient subsequently experienced an SAE of Grade 4 immune-mediated encephalitis, considered related to dostarlimab.

Part 1A, Cohort 1B: a patient with osteosarcoma, received treatment with niraparib 200 mg oral once daily and dostarlimab 3 mg/kg dose IV Q3W, experienced an SAE of Grade 3 cerebral haemorrhage, considered related to niraparib. A patient with osteosarcoma, received treatment with niraparib 200 mg oral once daily and dostarlimab 3 mg/kg dose IV Q3W, experienced an AE of Grade 4 thrombocytopenia, considered related to niraparib.

Part 1B, Cohort 1: a patient with neuroblastoma, received treatment with niraparib 100 mg oral once daily and dostarlimab 7.5 mg/kg dose IV Q3W, experienced an AE of Grade 3 anemia requiring transfusion, considered related to niraparib and dostarlimab and an AE of Grade 4 platelet count decreased, considered related to niraparib. A patient with neuroblastoma, received treatment with

niraparib 75 mg oral once daily and dostarlimab 7.5 mg/kg dose IV Q3W, developed an AE of Grade 3 low platelets, considered related to niraparib.

Part 2 Safety Run-in: a patient with osteosarcoma, received treatment with niraparib 75 mg oral once daily and dostarlimab 7.5 mg/kg dose IV Q3W, experienced an SAE of Grade 3 alanine aminotransferase increased, treated with ursodeoxycholic acid and persisted for ≥7 days. The SAE was considered related to niraparib and dostarlimab. A patient with osteosarcoma, received treatment with niraparib 200 mg oral once daily and dostarlimab 7.5 mg/kg dose IV Q3W, experienced an SAE of Grade 3 immune-mediated encephalitis considered related to dostarlimab, that occurred outside of the DLT period.

Table 18 Dose-limiting toxicities: Part 1A and Part 1B

	Number of Treated Participants	Number of DLT-evaluable participants	Number of participants with DLTs (%) [a]
Part 1A: Cohort 0 Niraparib tablet 100mg/Dostarlimab 3mg/kg	11	8	1 (13)
Part 1A: Cohort 1A Niraparib tablet 100mg/Dostarlimab 7.5mg/kg	7	6	1 (17)
Part 1A: Cohort 1B Niraparib tablet 200mg/Dostarlimab 3mg/kg	5	2	2 (100)
Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/Dostarlimab 7.5mg/kg	3	2	2 (100)

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation; DLT=dose-limiting toxicity.
Note: Part 1A: Cohort 2 did not open for enrollment.
a. Percentage is based on number of DLT-evaluable participants

Thrombocytopenia events leading to enrollment pause:

Six participants experienced events of Grade ≥3 thrombocytopenia (or platelet count decreased) which leading to enrollment pause in original Part 1B and Part 2B of the study, 3 out of 3 patients in Part 1B Cohort 1 plus 3 out of 7 patients in the Part 2B neuroblastoma expansion cohort that led to an enrollment pause in all cohorts of the study on 04 July 2023.

A total of 9 participants reported a Grade ≥3 TEAE of thrombocytopenia or platelet count decreased (see below table).

Table 19 Treatment-emergent Grade 3 and 4 Thrombocytopenia or platelet count decreased events in Part 1A, Part 1B, Part 2A and Part 2B

	Number of Treated Participants	Number of participants with events (%) [a]
Part 1A: Cohort 0 Niraparib tablet 100mg/Dostarlimab 3mg/kg	11	2 (18)
Part 1A: Cohort 1A Niraparib tablet 100mg/Dostarlimab 7.5mg/kg	7	0
Part 1A: Cohort 1B Niraparib tablet 200mg/Dostarlimab 3mg/kg	5	1 (20)
Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/Dostarlimab 7.5mg/kg	3	3 (100)
Part 2A Niraparib tablet 100mg/Dostarlimab 7.5mg/kg	11	0
Part 2B Niraparib tablet 100mg/Dostarlimab 7.5mg/kg	7	3 (43)

Note: Part 1A: Cohort 2 did not open for enrollment.
Includes Grade 3 and Grade 4 TEAEs of thrombocytopenia or platelet count decreased

Common adverse events:

All patients in Part 1 and Part 2 of the study had at least 1 TEAE. The most common TEAEs (≥40%) by cohort, by PT were the following (Table 20):

- Part 1A: anaemia and pyrexia in Cohort 0; alanine aminotransferase increased, anaemia, aspartate aminotransferase increased, headache, and vomiting in Cohort 1A; and anaemia, constipation, leukopenia, nausea, neutrophil count decreased, pain in extremity, thrombocytopenia, and vomiting in Cohort 1B.
- Part 1B: abdominal pain, alanine aminotransferase increased, anaemia, aspartate aminotransferase increased, lethargy, pain, and platelet count decreased.
- Part 2: abdominal pain, anaemia, aspartate aminotransferase increased, decreased appetite, leukopenia, neutrophil count decreased, pyrexia, thrombocytopenia and vomiting in Part 2B;

and anaemia, leukopenia, neutropenia, and thrombocytopenia in Part 2 Safety Run-in. There were no TEAEs occurring in ≥40% participants in Part 2A.

Table 20 Summary of Treatment Emergent Adverse Events (≥40% subjects in any Cohort by Preferred Term) by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**11 (100)**	**7 (100)**	**5 (100)**	**3 (100)**	**11 (100)**	**7 (100)**	**3 (100)**
Blood and lymphatic system disorders	**7 (64)**	**4 (57)**	**3 (60)**	**3 (100)**	**7 (64)**	**4 (57)**	**3 (100)**
Anaemia	7 (64)	3 (43)	2 (40)	3 (100)	3 (27)	3 (43)	2 (67)
Thrombocytopenia	2 (18)	0	2 (40)	1 (33)	1 (9)	3 (43)	2 (67)
Neutropenia	0	1 (14)	1 (20)	0	1 (9)	0	2 (67)
Leukopenia	0	2 (29)	2 (40)	0	2 (18)	0	3 (100)
Gastrointestinal disorders	**7 (64)**	**5 (71)**	**4 (80)**	**3 (100)**	**7 (64)**	**4 (57)**	**1 (33)**
Vomiting	3 (27)	4 (57)	2 (40)	1 (33)	3 (27)	3 (43)	0
Constipation	3 (27)	2 (29)	3 (60)	1 (33)	2 (18)	1 (14)	0
Abdominal pain	2 (18)	2 (29)	0	2 (67)	1 (9)	3 (43)	0
Nausea	0	2 (29)	3 (60)	1 (33)	2 (18)	2 (29)	0
General disorders and administration site conditions	**10 (91)**	**4 (57)**	**2 (40)**	**2 (67)**	**6 (55)**	**5 (71)**	**1 (33)**
Pyrexia	7 (64)	1 (14)	1 (20)	0	1 (9)	3 (43)	1 (33)
Pain	0	0	0	2 (67)	2 (18)	0	0
Investigations	**6 (55)**	**5 (71)**	**3 (60)**	**3 (100)**	**4 (36)**	**5 (71)**	**1 (33)**
Aspartate aminotransferase increased	0	3 (43)	1 (20)	2 (67)	1 (9)	3 (43)	1 (33)
Alanine aminotransferase increased	0	4 (57)	1 (20)	2 (67)	0	1 (14)	1 (33)
Platelet count decreased	2 (18)	1 (14)	1 (20)	2 (67)	1 (9)	2 (29)	0
Neutrophil count decreased	0	1 (14)	2 (40)	0	1 (9)	3 (43)	0
Musculoskeletal and connective tissue disorders	**6 (55)**	**3 (43)**	**2 (40)**	**2 (67)**	**2 (18)**	**2 (29)**	**0**
Pain in extremity	2 (18)	1 (14)	2 (40)	1 (33)	1 (9)	0	0

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Metabolism and nutrition disorders	**3 (27)**	**3 (43)**	**1 (20)**	**1 (33)**	**4 (36)**	**3 (43)**	**1 (33)**
Decreased appetite	2 (18)	2 (29)	1 (20)	0	3 (27)	3 (43)	0
Nervous system disorders	**2 (18)**	**4 (57)**	**1 (20)**	**3 (100)**	**3 (27)**	**2 (29)**	**1 (33)**
Headache	2 (18)	3 (43)	0	1 (33)	2 (18)	1 (14)	0
Lethargy	0	0	0	2 (67)	1 (9)	1 (14)	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

Grade 3 or 4 adverse events

Grade 3-4 TEAEs in Part 1A were reported higher in Cohort 0 (91%) and Cohort 1B (80%) compared to Cohort 1A (29%). In Part 1B, all patients experienced Grade ≥3 TEAE. In Part 2, Grade ≥3 TEAE were higher in Part 2B (71%), and Part 2 Safety Run-in (67%) compared to Part 2A (45%) [see table below].

The most common Grade ≥3 TEAEs in Part 1A Cohort 0 were anaemia (3 patients [27%]), and pain in extremity, platelet count decreased, and pleural effusion (2 patients [18%]) each); all other Grade ≥3 TEAEs were reported by one patient (9%) each. In Part 1A Cohort 1A, no more than one patient (14%) reported any Grade ≥3 TEAE each. In Part 1A Cohort 1B, the most common Grade ≥3 TEAE were neutrophil count decreased (2 participants [40%]); all other Grade ≥3 TEAEs were reported by one patient each (20%) [Table 21]. In Part 1B were anaemia (3 patients [100%]), and platelet count

decreased (2 patients [67%]); all other Grade ≥3 TEAEs were reported by one patient (33%) each [see table below].

In Part 2A, the most Grade ≥3 TEAEs were anaemia and febrile neutropenia (2 patients [18%] each); all other Grade ≥3 TEAEs were reported by one patient (9%) each. In Part 2 Safety Run-in, no more than one patient (33%) reported any Grade ≥3 TEAE each (Table 17). In Part 2B were anaemia and thrombocytopenia (2 participants [29%] each); all other Grade ≥3 TEAEs were reported by one patient (14%) each (see below table).

Table 21 Summary of Grade ≥3 Treatment Emergent Adverse Events (≥30% subjects in any Cohort by Preferred Term) by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**10 (91)**	**2 (29)**	**4 (80)**	**3 (100)**	**5 (45)**	**5 (71)**	**2 (67)**
Blood and lymphatic system disorders	**4 (36)**	**0**	**3 (60)**	**3 (100)**	**4 (36)**	**3 (43)**	**0**
Anaemia	3 (27)	0	1 (20)	3 (100)	2 (18)	2 (29)	0
Thrombocytopenia	0	0	1 (20)	1 (33)	0	2 (29)	0
Investigations	**2 (18)**	**0**	**2 (40)**	**2 (67)**	**1 (9)**	**3 (43)**	**1 (33)**
Platelet count decreased	2 (18)	0	0	2 (67)	0	1 (14)	0
Neutrophil count decreased	0	0	2 (40)	0	1 (9)	1 (14)	0
Alanine aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Aspartate aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Blood creatinine increased	0	0	0	1 (33)	0	0	0
Blood urea increased	0	0	0	1 (33)	0	0	0
Respiratory, thoracic and mediastinal disorders	**5 (45)**	**0**	**1 (20)**	**1 (33)**	**0**	**2(29)**	**0**
Epistaxis	1 (9)	0	0	1 (33)	0	1 (14)	0
Nervous system disorders	**0**	**1 (14)**	**1 (20)**	**2 (67)**	**1 (9)**	**0**	**1 (33)**
Immune-mediated encephalitis	0	1 (14)	0	0	0	0	1 (33)
Headache	0	0	0	1 (33)	0	0	0
Hypotonia	0	0	0	1 (33)	0	0	0
Lethargy	0	0	0	1 (33)	0	0	0
Trigeminal neuralgia	0	0	0	1 (33)	0	0	0
Metabolism and nutrition disorders	**0**	**1 (14)**	**0**	**1 (33)**	**0**	**0**	**1 (33)**
Hypokalemia	0	0	0	1 (33)	0	0	1 (33)
Vascular disorders	**0**	**0**	**0**	**0**	**0**	**0**	**1 (33)**
Hypertension	0	0	0	0	0	0	1 (33)

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, CTCAE=Common Terminology Criteria for Adverse Events, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0 and graded according to CTCAE v5.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

Drug-related adverse events

The most common (≥40% of participants) drug-related TEAEs within the cohorts were anaemia, thrombocytopenia, neutropenia, leukopenia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, neutrophil count decreased, nausea, vomiting, and decreased appetite (see table below).

Table 22 Summary of Drug-Related Treatment Emergent Adverse Events (≥40% subjects in any Cohort by Preferred Term) by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**8 (73)**	**6 (86)**	**4 (80)**	**3 (100)**	**11 (100)**	**7 (100)**	**3 (100)**
Blood and lymphatic system disorders	**5 (45)**	**3 (43)**	**3 (60)**	**2 (67)**	**5 (45)**	**4 (57)**	**3 (100)**
Anaemia	3 (27)	1 (14)	2 (40)	2 (67)	2 (18)	3 (43)	0
Thrombocytopenia	2 (18)	0	2 (40)	0	1 (9)	3 (43)	2 (67)
Leukopenia	0	2 (29)	2 (40)	0	2 (18)	0	3 (100)
Neutropenia	0	1 (14)	1 (20)	0	1 (9)	0	2 (67)
Investigations	**3 (27)**	**5 (71)**	**3 (60)**	**3 (100)**	**4 (36)**	**3 (43)**	**1 (33)**
Aspartate aminotransferase increased	0	3 (43)	1 (20)	2 (67)	1 (9)	3 (43)	1 (33)
Alanine aminotransferase increased	0	4 (57)	1 (20)	2 (67)	0	1 (14)	1 (33)
Platelet count decreased	1 (9)	1 (14)	1 (20)	2 (67)	1 (9)	2 (29)	0
Neutrophil count decreased	0	1 (14)	2 (40)	0	1 (9)	2 (29)	0
Gastrointestinal disorders	**2 (18)**	**3 (43)**	**2 (40)**	**1 (33)**	**4 (36)**	**3 (43)**	**0**
Nausea	0	1 (14)	2 (40)	1 (33)	1 (9)	2 (29)	0
Vomiting	0	2 (29)	0	1 (33)	1 (9)	3 (43)	0
Metabolism and nutrition disorders	**2 (18)**	**3 (43)**	**0**	**0**	**1 (9)**	**3 (43)**	**0**
Decreased appetite	2 (18)	2 (29)	0	0	1 (9)	3 (43)	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

A summary of Grade 3 or 4 TEAEs that were considered related to study treatment is provided below (see table below). The only drug-related Grade ≥3 TEAEs occurring in more than one patient in any cohort were anaemia, neutrophil count decreased, platelet count decreased, and thrombocytopenia.

Table 23 Summary of Drug-Related Grade ≥3 Treatment Emergent Adverse Events (≥20% subjects in any Cohort by Preferred Term) by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2 :Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**2 (18)**	**2 (29)**	**4 (80)**	**2 (67)**	**4 (36)**	**4 (57)**	**2 (67)**
Blood and lymphatic system disorders	**2 (18)**	**0**	**3 (60)**	**2 (67)**	**3 (27)**	**3 (43)**	**0**
Anaemia	1 (9)	0	0	2 (67)	1 (9)	2 (29)	0
Thrombocytopenia	0	0	1 (20)	0	0	2 (29)	0
Leukopenia	0	0	1 (20)	0	1 (9)	0	0
Lymphopenia	0	0	1 (20)	0	1 (9)	0	0
Neutropenia	0	0	1 (20)	0	1 (9)	0	0
Febrile neutropenia	0	0	0	0	1 (9)	0	0
Immune thrombocytopenia	1 (9)	0	0	0	0	0	0
Investigations	**1 (9)**	**0**	**2 (40)**	**2 (67)**	**1 (9)**	**2 (29)**	**1 (33)**
Platelet count decreased	1 (9)	0	0	2 (67)	0	1 (14)	0
Neutrophil count decreased	0	0	2 (40)	0	1 (9)	0	0
Alanine aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Aspartate aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Nervous system disorders	**0**	**1 (14)**	**1 (20)**	**0**	**1 (9)**	**0**	**1 (33)**
Immune-mediated encephalitis	0	1 (14)	0	0	0	0	1 (33)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2 :Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Cerebral haemorrhage	0	0	1 (20)	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, CTCAE=Common Terminology Criteria for Adverse Events, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0 and graded according to CTCAE v5.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

8.4. Deaths

A total of 21 patients died; 20 deaths occurred during the study, and one patient, enrolled in Part 2A, died following discontinuation from the study: 7 patients (64%) in Part 1A Cohort 0, 3 patients (43%) in Part 1A Cohort 1A and 3 patients (60%) in Part 1A Cohort 1B; 3 patients (100%) in Part 1B Cohort 1;1 patient (33%) in Part 2 Safety Run-in, 2 patients (18%) in Part 2A, and 2 patients (29%) in Part 2B.

The primary cause of death was cancer for all patients, apart from one patient in Part 1A Cohort 1A with cause of death 'other'. The cause of death 'other' was identified to be a Grade 5 event of immune-mediated encephalitis.

A total of 4 patients reported a TEAE which led to death; 3 patients (27%) in Part 1A Cohort 0 [pleural effusion, respiratory disorder, and respiratory failure (1 patient [9%]) each), and 1 patient (14%) in Part 1A Cohort 1A who reported an immune-mediated encephalitis.

8.5. Serious adverse events (SAEs)

SAEs reported in in Part 1A were higher in Part 1A Cohort 0 (55% of patients), compared with Part 1A Cohort 1A and Part 1A Cohort 1B (29% and 40% of patients, respectively). Two patients (67%) experienced a SAE in Part 1B. In Part 2, the percentage of patients experienced a SAE was higher in Part 2 Safety Run-in and Part 2B (67% and 57%, respectively), compared with Part 2A (36%). In all cohorts, no more than one patient reported any SAE each, except from Part 2B, where 2 participants (29%) each reported 2 SAEs of pyrexia.

Grade ≥3 SAE reported in Part 1A was higher in Part 1A Cohort 0 (55%), compared with Part 1A Cohort 1A and Part 1A Cohort 1B (14% and 20%, respectively). Two patients (67%) experienced Grade ≥3 SAEs in Part 1B. In Part 2, Grade ≥3 SAEs were higher in Part 2 Safety Run-in and Part 2B (67% and 57%, respectively), compared with Part 2A (18%) [see table below].

Table 24 Summary of Grade ≥3 Serious Treatment Emergent Adverse Events by Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2: Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**6 (55)**	**1 (14)**	**1 (20)**	**2 (67)**	**2 (18)**	**4 (57)**	**2 (67)**
Alanine aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Anaemia	0	0	0	0	0	1 (14)	0
Aspartate aminotransferase increased	0	0	0	0	0	1 (14)	0
Cerebral haemorrhage	0	0	1 (20)	0	0	0	0
COVID-19	1 (9)	0	0	0	0	1 (14)	0
Dyspnoea	0	0	0	0	0	1 (14)	0
Epistaxis	0	0	0	1 (33)	0	1 (14)	0
Febrile neutropenia	0	0	0	0	1 (9)	0	0
Hypotonia	0	0	0	1 (33)	0	0	0
Immune-mediated encephalitis	0	1 (14)	0	0	0	0	1 (33)
Immune thrombocytopenia	1 (9)	0	0	0	0	0	0
Lethargy	0	0	0	1 (33)	0	0	0
Nausea	0	1 (14)	0	0	0	0	0
Pain in extremity	1 (9)	0	0	0	0	0	0
Platelet count decreased	1 (9)	0	0	0	0	1 (14)	0
Pleural effusion	1 (9)	0	0	0	0	0	0
Pyrexia	0	0	0	0	1 (9)	1 (14)	0
Respiratory disorder	1 (9)	0	0	0	0	0	0
Respiratory failure	1 (9)	0	0	0	0	0	0
Vomiting	0	1 (14)	0	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, CTCAE=Common Terminology Criteria for Adverse Events, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0 and graded according to CTCAE v5.0.
Note: If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for the preferred term under the highest CTCAE grade available per that preferred term

Drug-related SAE reported in Part 1A was higher in Cohort 1A (2 patients [29%]) and Cohort 1B (1 patient [20%]), compared with Cohort 0 (1 patient [9%]). In Part 2, drug-related SAEs were higher in Part 2 Safety Run-in (2 patients [67%]) compared with Part 2A (1 patient [9%]) and Part 2B (2 patients [29%]). One patient (33%) reported a drug-related SAE in Part 1B.

Drug-related SAEs in at least 1 cohort were: anaemia, immune thrombocytopenia, platelet count decreased, abdominal pain, aspartate aminotransferase increased, alanine aminotransferase increased, immune-mediated encephalitis, cerebral haemorrhage, headache, hyponatremia, nausea, vomiting, blood creatinine increased, and sinus tachycardia.

Related SAEs reported as immune-mediated encephalitis were experienced by 2 patients. One of these events was not considered related to dostarlimab as the event was not typical for checkpoint inhibitor immune-mediated encephalitis, and acute disseminated encephalomyelitis secondary to viral upper respiratory infection and viral encephalitis represented potential alternative explanations in this case.

A related SAE of cerebral haemorrhage considered related to niraparib by the investigator was reported in one patient. An MRI scan showed cerebral metastasis, which could explain the cerebral haemorrhage associated to thrombopenia due to the investigational products. It was considered the event of cerebral haemorrhage was not likely related to either niraparib or dostarlimab. The participant's cerebral metastasis was considered a confounding factor.

Discontinuation due to adverse events

The percentage of patients who experienced any TEAE leading to discontinuation of study drug was higher in Part 1A Cohort 0 (3 patients [27%]), compared with Cohort 1A and Cohort 1B (one patient each [14%, and 20%, respectively]). In Part 1B, 2 patients (67%) experienced any TEAE leading to discontinuation of study drug (Table 25). In Part 2, the percentage of participants experiencing any TEAE leading to discontinuation of study drug was higher in Part 2 Safety Run-in and Part 2B (2 participants [67%] and 3 participants [43%], respectively), compared with Part 2A (2 participants [18%]).

In Part 1B, 2 patients (67%) reported a TEAE of platelet count decreased which led to discontinuation of study drug. In Part 2B, 2 patients (29%) reported a TEAE of thrombocytopenia which led to discontinuation of study drug. In all Part 1A cohorts, Part 2A, and Part 2 Safety Run-in, no more than one patient reported any TEAE leading to discontinuation of study drug each (see table below).

Table 25 Summary of Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2:Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**3 (27)**	**1 (14)**	**1 (20)**	**2 (67)**	**2 (18)**	**3 (43)**	**2 (67)**
Investigations	**1 (9)**	**0**	**0**	**2 (67)**	**0**	**1 (14)**	**1 (33)**
Platelet count decreased	1 (9)	0	0	2 (67)	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Nervous system disorders	**0**	**1 (14)**	**1 (20)**	**0**	**1 (9)**	**0**	**1 (33)**
Immune-mediated encephalitis	0	1 (14)	0	0	0	0	1 (33)
Cerebral haemorrhage	0	0	1 (20)	0	0	0	0
Spinal cord compression	0	0	0	0	1 (9)	0	0
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**1 (9)**	**2 (29)**	**0**
Thrombocytopenia	0	0	0	0	1 (9)	2 (29)	0
Respiratory. thoracic and mediastinal disorders	**1 (9)**	**0**	**0**	**0**	**1 (9)**	**0**	**0**
Dyspnoea	0	0	0	0	1 (9)	0	0
Respiratory disorder	1 (9)	0	0	0	0	0	0
Infections and infestations	**1 (9)**	**0**	**0**	**0**	**0**	**0**	**0**
COVID-19	1 (9)	0	0	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

The percentage of patients who experienced any drug-related TEAE leading to discontinuation of study drug was similar across all Part 1A cohorts (one patient each [Cohort 0, 9%, Cohort 1A, 14% and Cohort 1B, 20%, respectively]). In Part 1B, 2 patients (67%) reported a drug-related TEAE of platelet count decreased which led to discontinuation of study drug. In Part 2, this percentage was higher in Part 2 Safety Run-in and Part 2B (2 patients [67%] and 3 patients [43%], respectively), compared with Part 2A (2 patients [18%]) (see table below).

Drug-related TEAEs leading to discontinuation of study drug in at least 1 cohort were platelet count decreased, alanine aminotransferase increased, immune-mediated encephalitis, cerebral hemorrhage, spinal cord compression, thrombocytopenia, and dyspnoea (see below table).

Table 26 Summary of Drug-related Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2 Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**1 (9)**	**1 (14)**	**1 (20)**	**2 (67)**	**2 (18)**	**3 (43)**	**2 (67)**
Investigations	**1 (9)**	**0**	**0**	**2 (67)**	**0**	**1 (14)**	**1 (33)**
Platelet count decreased	1 (9)	0	0	2 (67)	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	1 (14)	1 (33)
Nervous system disorders	**0**	**1 (14)**	**1 (20)**	**0**	**1 (9)**	**0**	**1 (33)**
Immune-mediated encephalitis	0	1 (14)	0	0	0	0	1 (33)
Cerebral haemorrhage	0	0	1 (20)	0	0	0	0
Spinal cord compression	0	0	0	0	1 (9)	0	0
Blood and lymphatic system disorders	**0**	**0**	**0**	**0**	**1 (9)**	**2 (29)**	**0**
Thrombocytopenia	0	0	0	0	1 (9)	2 (29)	0
Respiratory. thoracic and mediastinal disorders	**0**	**0**	**0**	**0**	**1 (9)**	**0**	**0**
Dyspnoea	0	0	0	0	1 (9)	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject was counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject was counted only once for that preferred term.

8.6. Adverse events leading to dose reduction, interruption or delay

TEAEs leading to dose reduction of niraparib were reported in 2 patients, 1 patient (14%) in Part 1A Cohort 1A (TEAEs of nausea, headache, and vomiting), and 1 patient (20%) in Part 1A Cohort 1B (a TEAE of neutrophil count decreased) (see below table). Dose reductions were not allowed for dostarlimab, per protocol.

Table 27 Summary of Treatment Emergent Adverse Events Leading to Dose Reduction for Niraparib by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2 Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**0**	**1 (14)**	**1 (20)**	**0**	**0**	**0**	**0**
Gastrointestinal disorders	**0**	**1 (14)**	**0**	**0**	**0**	**0**	**0**
Nausea	0	1 (14)	0	0	0	0	0
Vomiting	0	1 (14)	0	0	0	0	0
Investigations	**0**	**0**	**1 (20)**	**0**	**0**	**0**	**0**
Neutrophil count decreased	0	0	1 (20)	0	0	0	0
Nervous system disorders	**0**	**1 (14)**	**0**	**0**	**0**	**0**	**0**
Headache	0	1 (14)	0	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

Patients in all cohorts in Part 1A, Part 1B, and Part 2 experienced a TEAE which led to dose interruption for niraparib (Table 28). In Part 1A Cohort 0, TEAEs of platelet count decreased and COVID-19 were reported by 2 patients (18%) each (see below table).

Table 28 Summary of Treatment Emergent Adverse Events Leading to Dose Interruption/Infusion Delay for Niraparib by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2 Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**4 (36)**	**2 (29)**	**4 (80)**	**2 (67)**	**3 (27)**	**4 (57)**	**1 (33)**
Blood and lymphatic system disorders	**2 (18)**	**0**	**1 (20)**	**1 (33)**	**3 (27)**	**1 (14)**	**1 (33)**
Thrombocytopenia	1 (9)	0	0	1 (33)	1 (9)	1 (14)	1 (33)
Neutropenia	0	0	1 (20)	0	1 (9)	0	0
Investigations	**2 (18)**	**1 (14)**	**2 (40)**	**1 (33)**	**1 (9)**	**2 (29)**	**0**
Platelet count decreased	2 (18)	1 (14)	1 (20)	1 (33)	0	1 (14)	0
Neutrophil count decreased	0	0	1 (20)	0	1 (9)	0	0
Alanine aminotransferase increased	0	0	0	0	0	1 (14)	0
Aspartate aminotransferase increased	0	0	0	0	0	1 (14)	0
Blood creatinine increased	0	0	0	0	0	1 (14)	0
Blood urea increased	0	0	0	0	0	1 (14)	0
Infections and infestations	**2 (18)**	**0**	**0**	**0**	**0**	**1 (14)**	**0**
COVID-19	2 (18)	0	0	0	0	1 (14)	0
Gastrointestinal disorders	**1 (9)**	**1 (14)**	**0**	**0**	**0**	**0**	**0**
Nausea	0	1 (14)	0	0	0	0	0
Vomiting	0	1 (14)	0	0	0	0	0
General disorders and administration site conditions	**1 (9)**	**0**	**0**	**0**	**0**	**1 (14)**	**0**
Pyrexia	0	0	0	0	0	1 (14)	0
Nervous system disorders	**1 (9)**	**1 (14)**	**0**	**0**	**0**	**0**	**0**
Headache	1 (9)	1 (14)	0	0	0	0	0
Seizure	0	1 (14)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**1 (9)**	**0**	**1 (20)**	**0**	**0**	**0**	**0**
Hypoxia	0	0	1 (20)	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject is counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject is counted only once for that preferred term.

Patients in all cohorts of Part 1A experienced a TEAE which led to dose interruption/infusion delay for dostarlimab. In Part 1A Cohort 0, a TEAE of COVID-19 was reported by 2 participants (18%). Across all other cohorts, no more than one patient reported any drug-related TEAE leading to dose interruption/infusion delay of dostarlimab. No patients in either Part 1B or Part 2 Safety Run-in reported a TEAE which led to dose interruption/infusion delay for dostarlimab. In Part 2A and Part 2B, one patient in each cohort (9% and 14%, respectively) reported a TEAE which led to interruption/infusion delay for dostarlimab (Table 29).

Drug-related TEAEs leading to dose interruption/infusion delay for dostarlimab were reported in 5 patients; 1 patient (9%) in Part 1A Cohort 0 (TEAE of anaemia), 1 patient (14%) in Part 1A Cohort 1A (TEAE of nausea), 1 patient (20%) in Part 1A Cohort 1B (TEAE of thrombocytopenia), 1 patient (9%) in Part 2A (TEAE of neutropenia) and 1 patient (14%) in Part 2B (TEAE of throat irritation).

Table 29 Summary of Treatment Emergent Adverse Events Leading to Dose Interruption/Infusion Delay for Dostarlimab by System Organ Class and Preferred Term (Safety Population)

n (%)	Part 1A: Cohort 0 Niraparib tablet 100mg/ dostarlimab 3mg/kg N=11	Part 1A: Cohort 1A Niraparib tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 1A: Cohort 1B Niraparib tablet 200mg/ dostarlimab 3mg/kg N=5	Part 1B: Cohort 1 Niraparib AAOLF (age-based dose)/ dostarlimab 7.5mg/kg N=3	Part 2A: Osteosarcoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=11	Part 2B: Neuroblastoma Niraparib Tablet 100mg/ dostarlimab 7.5mg/kg N=7	Part 2 Safety Run-in Niraparib TfOS (weight-based dose)/ dostarlimab 7.5mg/kg N=3
Any Event	**3 (27)**	**1 (14)**	**1 (20)**	**0**	**1 (9)**	**1 (14)**	**0**
Blood and lymphatic system disorders	**1 (9)**	**0**	**1 (20)**	**0**	**1 (9)**	**0**	**0**
Anaemia	1 (9)	0	0	0	0	0	0
Neutropenia	0	0	0	0	1 (9)	0	0
Thrombocytopenia	0	0	1 (20)	0	0	0	0
Infections and infestations	**2 (18)**	**0**	**0**	**0**	**0**	**0**	**0**
COVID-19	2 (18)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**0**	**1 (20)**	**0**	**0**	**1 (14)**	**0**
Hypoxia	0	0	1 (20)	0	0	0	0
Throat irritation	0	0	0	0	0	**1 (14)**	**0**
Gastrointestinal disorders	**0**	**1 (14)**	**0**	**0**	**0**	0	0
Nausea	0	1 (14)	0	0	0	0	0
General disorders and administration site conditions	**0**	**1 (14)**	**0**	**0**	**0**	**0**	**0**
Hyperthermia	0	1 (14)	0	0	0	0	0

Abbreviations: AAOLF=Age-appropriate Oral Liquid Formulation, TfOS=Tablet for Oral Suspension.
Note: Adverse event terms are coded according to MedDRA v28.0.
Note: If a subject experienced more than 1 event in a given system organ class, that subject was counted once for the system organ class. If a subject experienced more than 1 event with a given preferred term, that subject was counted only once for that preferred term.
Note: Infusion interruption refers to halting treatment to manage reactions occurring during its administration. Infusion delay refers to administering treatment outside of schedule to manage adverse events.

8.7. Adverse Events of Special Interest (AESIs)

No AESIs were reported for any patient administered niraparib during the study. AESIs for niraparib were defined as follows:

- MDS and AML (MedDRA Criteria for Selection of PTs: Myelodysplastic syndrome SMQ [Narrow] and Leukemias acute myeloid [high level term].)
- Second primary malignancy (new malignancies [other than MDS or AML]) (MedDRA Criteria for Selection of PTs: Hematological malignant tumors SMQ (Narrow), Non-hematological malignant tumors SMQ (Narrow), excluding terms not reflecting a new malignancy, e.g., signs or symptoms of malignancies, disease progression of existing cancer).

No AESIs were defined for dostarlimab, according to the protocol.

Immune-mediated Adverse Events (imAE)

A total of 17 out of 47 patients treated across all cohorts (36%) had a dostarlimab-related imAE; 2 patients (18%) in Part 1A Cohort 0, 5 patients (71%) in Part 1A Cohort 1A, 2 patients (67%) in Part 1B Cohort 1, 2 patients (67%) in Part 2 Safety Run-in, 2 patients (18%) in Part 2A, and 4 patients (57%) in Part 2B. A total of 7 dostarlimab-related imAEs reported by 5 patients (11%) were Grade ≥3 or serious imAE. One patient in Part 1A Cohort 0 (9%) reported Grade 4 immune thrombocytopenia. One patient in Part 1A Cohort 1A (14%) reported a Grade 5 imAE of immune mediated encephalitis which led to discontinuation of dostarlimab. One patient in Part 2 Safety Run-in reported Grade 3 immune-mediated encephalitis which led to discontinuation of dostarlimab. The remaining 4 Grade ≥3 imAEs included 1 event each of Grade 3 aspartate aminotransferase increased and Grade 3 alanine aminotransferase increased in one patient in Part 2B and 1 event each of Grade 3 aspartate aminotransferase increased and Grade 3 alanine aminotransferase increased in one patient in Part 2 Safety Run in.

The most common imAEs for dostarlimab were alanine aminotransferase increased (4 patients [57%] in Part 1A Cohort 1A, 2 patients [67%] in Part 1B, 1 patient [14%] in Part 2B, 1 patient [33%] in Part 2 Safety Run-in), and aspartate aminotransferase increased (3 patients [43%] in Part 1A Cohort 1A, 2 patients [67%] in Part 1B Cohort 1, 1 patient [9%] in Part 2A, 3 patients [43%] in Part 2B, 1 patient [33%] in Part 2 Safety Run-in).

8.8. Adverse Drug Reactions

No new adverse drug reactions were identified from this study.

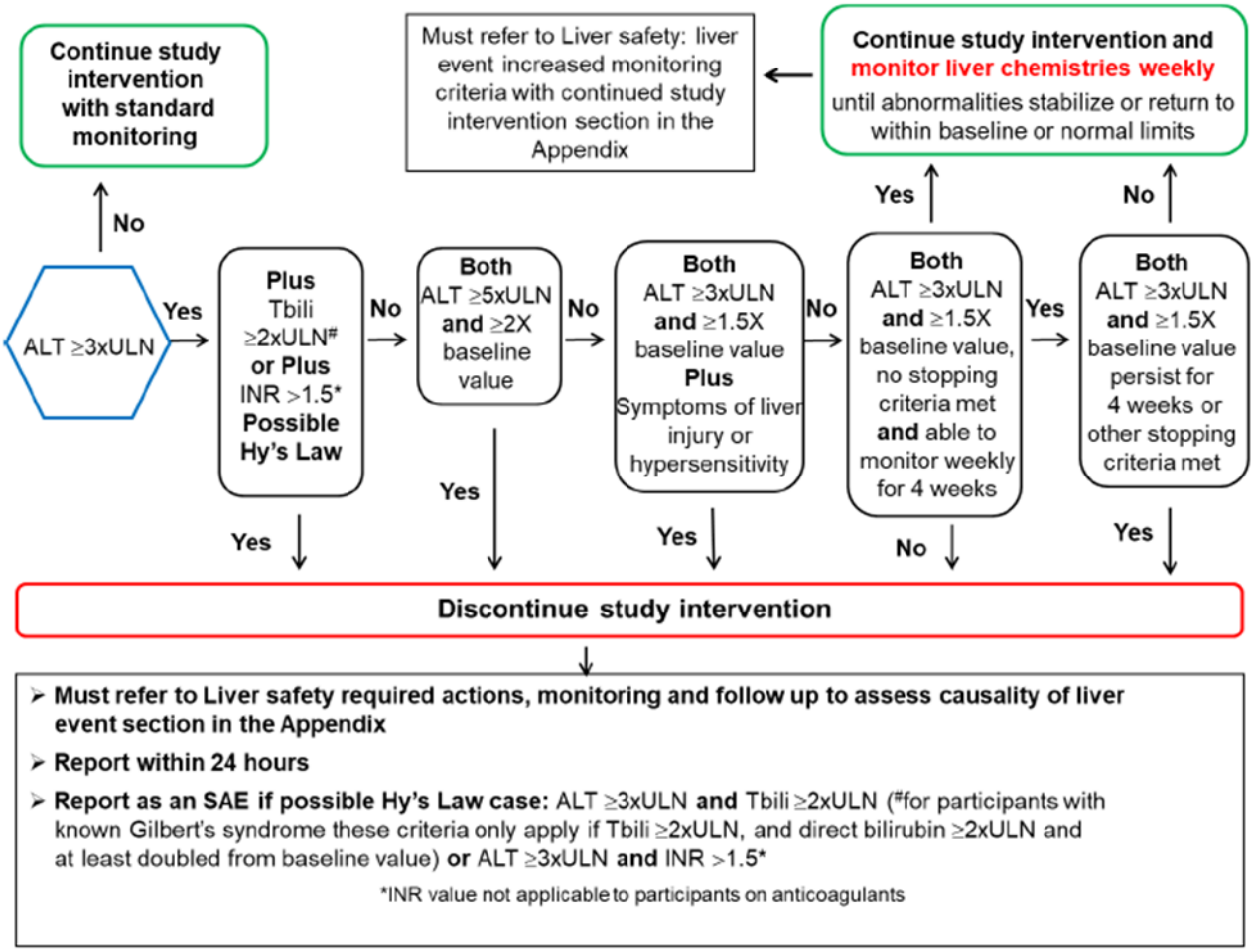
8.9. Laboratory findings

Regarding haematology laboratory abnormalities during treatment, a grade shift in anaemia to Grade 3 was reported in 5 patients (45%) in Part 1A Cohort 0, 1 patient (14%) in Part 1A Cohort 1A, 1 patient (20%) in Part 1A Cohort 1B, all 3 patients (100%) in Part 1B, 1 patient (10%) in Part 2A, and 2 patients (29%) in Part 2B. No patients reported grade shift in anaemia to Grade 4. A grade shift in neutrophil count decreased to Grade 3 was reported in 1 patient (20%) in Part 1A Cohort 1B, 1 patient (33%) in Part 1B Cohort 1, 2 patients (20%) in Part 2A, and 1 patient (14%) in Part 2B. One patient (20%) in Part 1A Cohort 1B, and 1 patient (10%) in Part 2A reported a grade shift in neutrophil count decreased to Grade 4.

Any abnormal chemistry test results assessed as clinically significant were to be reported as TEAEs.

Liver stopping events were reported in 2 patients, 1 patient in Part 2B (neuroblastoma expansion cohort) and 1 patient in the Part 2 Safety Run-in. Both events were reported as resolved. No participant met the criteria for a possible Hy’s law event.

Figure 4 Phase I/II Liver Chemistry Stopping and Monitoring Event Algorithm



Any abnormal vital signs as well as any abnormal ECG measurements assessed as clinically significant were to be reported as TEAEs. Minor changes in ECG parameters were observed during the clinical study, but no trend was identified for any of the parameters. No participants met the QTc stopping criterion (QTc >500 msec).

8.10. Safety in Special populations

Due to limited data available from the 47 participants recruited into the SCOOP study before the early termination, the evaluation of safety in special groups and situations was not possible.

9. Discussion on clinical efficacy and safety

Study SCOOP (213406), which is part of a PIP (study 1), is a phase 1, multicenter, open-label, dose escalation (Part 1) and dose expansion study (Part 2) of niraparib and dostarlimab in paediatric patients from 5 years of age to less than 18 years of age with recurrent or refractory (R/R) solid tumours, excluding central nervous system (CNS) tumours in Part 1A and 1B, and with R/R osteosarcoma and R/R neuroblastoma in Part 2.

Niraparib was administered orally daily in combination with dostarlimab administered via IV infusion once every 3 weeks (maximum 500 mg). Niraparib was supplied as dispersible tablets referred as age-appropriate oral liquid formulation (AAOLF) in Part 1B under protocol amendment 03 (and earlier) and as tablet for oral suspension (TfOS) in Part 1B and Part 2 of the study under protocol amendment 04.

Part 1A of the study is comprised of three cohorts included participants who were able to swallow the 100 mg niraparib tablets and who had a body weight of ≥20 kg: cohort 0 (n=11), cohort 1A (n=7) and cohort 1B (n=5). The cohort 0 subjects received niraparib tablets 100 mg and dostarlimab 3 mg/Kg. The cohort 1A subjects received niraparib tablets 100 mg and dostarlimab 7.5 mg/Kg. The cohort 1B subjects received niraparib tablets 200 mg and dostarlimab 3 mg/Kg.

Part 1B of the study is comprised of one cohort only, cohort 1 (n=3), included patients who could not swallow the 100 mg niraparib tablets or who had a body weight of <20 kg. The cohort 1 subjects received niraparib age-appropriate oral liquid formulation (AAOLF) age-based dose and dostarlimab 7.5 mg/kg.

Part 2 of the study (dose expansion) is comprised of two cohorts: the osteosarcoma expansion cohort (Part 2A, n=11) and the neuroblastoma expansion cohort (Part 2B, n=7). The Part 2A and Part 2B subjects received niraparib tablet 100 mg and dostarlimab 7.5 mg/kg, the RP2D determined in Part 1A.

Part 2 Safety Run-in cohort (n=3) was introduced under the amendment 04, included patients 8 years and older to less than 18 years of age who had a body weight ≥20 kg and able to swallow 100 mg niraparib tablets. These patients received a weight-based niraparib tablet for oral suspension (TfOS) dosing regimen and dostarlimab 7.5 mg/kg prior to potential further enrollment into disease-specific expansion cohorts.

The dose regimens for niraparib in Part 1B and Part 2 were modified (introduction of a modified age-based dosing in less than 8 years and weight-based dosing in children older than 8 years) and a Part 2 Safety Run-in cohort was introduced, following study enrolment pause on 04 July 2023 (enrolment on Part 1A was completed), based on safety concerns (six events of unmanageable Grade ≥3 thrombocytopenia related TEAEs reported in Part 1B and in the Part 2 neuroblastoma expansion cohort). These modifications were introduced via study 213406 protocol amendment 4 dated 23 May 2024 and the study restarted in October 2024. Following restart (in October 2024), three additional patients were dosed according to the new scheduled, with one patient experiencing a Grade 3 immune-mediated encephalitis and one patient with a DLT (Grade 3 ALT increase); all three patients experienced progression disease. Immune-mediated encephalitis experienced by 2 participants, led to the review of study data, after which it was decided to end the study. The study was early terminated on 23 April 2025 (date of Last Subject Last Visit) based on these class specific toxicities and lack of meaningful activity with Part 2 expansion cohort ongoing.

The study protocol has been amended 5 times, the most notably amendment was amendment 04 (23 May 2024) which modified dose regimens and the study design.

The doses of niraparib and dostarlimab were based on adult's reference model. The dose calculations were based on body weight assessed at baseline. The starting dose of niraparib for paediatric participants who can swallow the 100 mg tablet and have a baseline body weight of ≥20 kg was determined based on allometric scaling to achieve exposures similar to the 200 mg daily dose in adults. The modified niraparib dosing regimens based on the final combined popPK/PD model were simplified to age-based dosing for paediatric population <8 years of age and weight-based dosing for children ≥8 to <18 years. The dose of dostarlimab was determined in Part 1A, the 7.5 mg/kg Q3W dose (with a maximum of 500 mg) was expected by allometric scaling to achieve exposures similar to the 500 mg Q3W dose in adults.

The inclusion and exclusion criteria are consistent with the disease. However, there was a lack of a biomarker selected population which complicates the interpretation of efficacy and translation into clinical practice. The BRCAness mutational signature was requested but not required for enrolment in Part 2 of the study. In Part 1, BRCAness mutational signature was required, the initial dose escalation was conducted in patients with tumours that are known to have a high frequency of BRCAness mutational signature (osteosarcoma, neuroblastoma, adrenocortical carcinoma, Ewing sarcoma, or rhabdomyosarcoma) or any other solid tumour (excluding CNS tumours) with confirmed BRCAness mutational signature.

Neither dostarlimab nor niraparib are indicated in the paediatric population currently. The SCOOP study was the initial study evaluating the combination of both niraparib and dostarlimab in paediatric participants.

A total of 50 paediatric subjects were enrolled into the study, 3 subjects were not assigned to any cohort and 47 patients were treated: 23 in Part 1A, 3 patients in Part 1B, 11 in Part 2A, 7 in Part 2B, and 3 patients in Part 2 Safety Run-in.

Baseline characteristics of all treated paediatric subjects were consistent with those of a paediatric patient population with R/R solid tumour (excluding tumours of the CNS).

While the inclusion criteria included paediatric patients from ≥6 months to <18 years of age, the study only included children from 5 years to <18 years of age. The median age of paediatric subjects was 14 years (adolescent age group), however in patients with neuroblastoma (3 subjects in Part 1B and 7 subjects in Part 2B) the median age was lower, 6 years and 10 years respectively. The mean Karnofsky performance status was 93.3% in total [80.0%, 96.7%, 100%, 96.7% in Cohort 0, Cohort 1A, Cohort 1B and Cohort 2A respectively]. The mean Lansky status was 91.6% in total [93.3%, 92.5%, 92.5%, 96.7%, 85.0%, 94.3%, 90.0% in Cohort 0, Cohort 1A, Cohort 1B, Cohort 2A and Cohort 2B, and Safety Run-in cohort respectively].

Most paediatric subjects had Stage IV disease at the study entry: 10 (91%) subjects in Cohort 0 (Part 1A), 7 (100%) subjects in Cohort 1 (Part 1A), 5 (100%) subjects in Cohort 1B (Part 1A), 3 (100%) subjects in Cohort 1 (Part 1B), 7 (64%) in osteosarcoma cohort (Part 2A), 7 (100%) in neuroblastoma cohort (Part 2B), and 3 (100%) in Safety Run-in cohort (Part 2). One patient in osteosarcoma cohort had missing stage of tumour at screening.

According to inclusion criteria patients must not have been eligible for alternative curative treatment. The majority of patients had 2 lines of anticancer therapy previously [6 (55%) in Cohort 0 (Part 1A), 3 (60%) Cohort 1B (Part 1A), 8 (73%) in osteosarcoma cohort (Part 2A), and 3 (100%) in the Safety Run-in cohort (Part 2)]. Three (43%) patients in Cohort 1A (Part 1A) and 2 (67%) patients in Cohort 1 (Part 1B) had ≥5 and lines or previous therapy respectively. In neuroblastoma cohort, three lines of therapy had been received by 2 patients (29%), four lines by 2 patients (29%), and five lines or more by 2 patients (29%).

Regarding the efficacy results prior to the study early termination, the SCOOP study did not meet its primary endpoint, a response was not reported for any of the 9 patients included in osteosarcoma expansion cohort (Part 2A) (PFS6 of 0%, 95% CI [0.0%, 33.6%]), and the 8 patients included in neuroblastoma expansion cohort (Part 2B) (ORR of 0%, 95% CI [0.0%, 36.9%]) in the mITT population (those Part 1 participants who satisfied the inclusion and exclusion criteria of Part 2 and were treated in Part2 cohort expansion), all reported progressive disease or death before 6 months. Consequently, the efficacy of niraparib in combination with dostarlimab in paediatric patients with R/R solid tumours, excluding central nervous system (CNS) was lacking and given the DLTs occurred an issue of underdosing can not be excluded.

With regard to safety data, the median duration of exposure was limited, 2.04 months or fewer for niraparib and 2 months or lower for dostarlimab, regardless of part or cohort.

DLTs were experienced by 7 patients in total, 4 out of 16 DLT-evaluable patients in Part 1A (25%), 2 out of 2 DLT-evaluable patients (100%) in original Part 1B, and 1 of 3 DLT-evaluable patients (33%) in Part 2 Safety Run-in

A total of 9 patients, 3 patients in Part 1B and 3 patients in Part 2B, all with neuroblastoma tumour type, reported six events of Grade ≥3 TEAE of thrombocytopenia or platelet count decreased, which led to an enrollment pause in all cohorts of the study on 04 July 2023.

All patients experienced at least one AE. Regarding drug-related AEs, the most commonly (≥40%) reported within any cohort were anemia, thrombocytopenia, neutropenia, leukopenia, aspartate aminotransferase increased, alanine aminotransferase increased, platelet count decreased, neutrophil count decreased, nausea, vomiting and decreased appetite.

Grade 3 or 4 TEAEs (≥20% subjects in any cohort) that were considered related to study treatment were anaemia [2 (67%) in Part 1B, 1 (9%) in Part 2A, 2 (29%) in Part 2B], thrombocytopenia [1 (20%) in Part 1A Cohort 1B, 2 (29%) in Part 2B], platelet count decreased [1 (9%) in Part 1A Cohort 0, 2 (67%) in Part 1B, 1 (14%) in Part 2B], and neutrophil count decreased [2 (40%) in Part 1A Cohort 1B, 1 (9%) in Part 2A].

Deaths occurred in 21 (44.68%) patients, 20 during the study reporting period and one following discontinuation from the study. Cancer was the cause of death for all patients except one who died due to an immune-mediated encephalitis. AEs with outcome of death were reported in 4 patients: 3 patients (27%) in Part 1A Cohort 0 [pleural effusion, respiratory disorder, and respiratory failure (1 patient [9%]) each), and 1 patient (14%) in Part 1A Cohort 1A who reported an immune-mediated encephalitis considered related to study drug.

None of the Grade 3-4 SAEs were reported in > 1 subject in all treated paediatric subjects. The SAEs that were reported in > 1 subjects were immune-mediated encephalitis reported by 2 patients, one (14%) in Cohort 1A (Part 1A) and one (33%) in Safety Run-in Cohort (Part 2). One of these two SAE of Grade 4 immune-mediated encephalitis was considered related to dostarlimab (patient in osteosarcoma cohort, Part 2A). A related SAE of Grade 3 cerebral haemorrhage considered related to niraparib by the investigator was reported in one patient (20%) in Cohort 1B (Part 1A). SAEs of Grade 3 nausea and Grade 3 vomiting considered related to niraparib was reported in one patient (14%) in Cohort 1A, and an AE of Grade 3 anorexia considered related to niraparib and dostarlimab. SAE of Grade 3 alanine aminotransferase increased (patient in osteosarcoma cohort, Part 2A) was considered related to niraparib and dostarlimab.

Drug-related SAE reported in Part 1A was higher in Cohort 1A (2 patients [29%] reported immune-mediated encephalitis and headache) and Cohort 1B (1 patient [20%]) reported cerebral haemorrhage), compared with Cohort 0 (1 patient [9%] reported platelet count decreased and immune thrombocytopenia). In Part 2, drug-related SAEs were higher in Part 2 Safety Run-in (2 patients [67%] reported ALT increased and immune-mediated encephalitis) compared with Part 2A (1 patient [9%]) and Part 2B (2 patients [29%] ALT increased, AST increased, blood creatine increased, anaemia). One patient (33%) reported a drug-related SAE (abdominal pain) in Part 1B.

Drug-related TEAEs leading to discontinuation of study drug in at least 1 cohort were platelet count decreased (one patient in Cohort 0, two patients in Cohort 1), alanine aminotransferase increased (one patient in Part 2B and one patient in Part 2 Safety Run-in), immune-mediated encephalitis (one patient in Cohort 1A and one patient in Part 2 Safety Run-in), cerebral haemorrhage (one patient in Cohort

1B), spinal cord compression (one patient in Part 2A), thrombocytopenia (one patient in Part 2A and two patients in Part 2B), and dyspnea (one patient in Part 2A).

A total of 17 patients had a dostarlimab related imAE, with 5 of the 17 reported a serious imAE, including 2 patients with immune mediated encephalitis. The frequency of these events was higher than observed in the adult population.

The safety profile of the combination in the paediatric population cannot be considered established due to the limited number of paediatric patients evaluated with limited exposure and the early termination of the study based on safety concerns. No new safety concerns were identified during the study. However, the toxicity profile is considered severe with 2 paediatric patients who had an immune mediated encephalitis (a well described side effect following checkpoint inhibitor treatment), one of the two immune mediated encephalitis was considered related to dostarlimab; and 6 paediatric patients who experienced an unmanageable Grade 3-4 thrombocytopenia (a known class side effect of PARP 1/2 inhibitors as niraparib) from a total of 47 paediatric patients treated that received combination treatment of niraparib plus dostarlimab.

The SmPC of Jemperli and Zejula have been updated based on the submitted results of the SCOOP study.

10. Changes to the Product Information

As a result of this variation, sections 4.2, 5.1 and 5.2 of the SmPC of Jemperli are being updated. The Package Leaflet (PL) is updated accordingly.

As a result of this variation, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC of Zejula are being updated. The PL is updated accordingly.

11. Request for supplementary information

11.1. Major objections

Clinical aspects

None.

11.2. Other concerns

Clinical aspects

1. The MAH is required to submit a table that compares the observed and predicted values at the same time points in order to facilitate the assessment of the similarity between the data sets.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

Non-clinical aspects

None.

Clinical aspects

None.

12.2. Other concerns

Clinical aspects

Question 1

The MAH is required to submit a table that compares the observed and predicted values at the same time points in order to facilitate the assessment of the similarity between the data sets.

Summary of the MAH's response

As per the Other Consideration included in the Rapporteur's final Assessment Report, the requested summary table that compares the observed and predicted values is presented below. The descriptive plot (Fig 3 m2.7.2) and table below compare the adult predictions with the paediatric observations at the planned time, not at the actual observation time. A dose-normalized plot using actual observation time of the individual PK samples (figure below) also supports that dostarlimab exposures were generally consistent with those seen in adults.

Assessment of the MAH's response

The pharmacokinetic (PK) data submitted for pediatric subjects enrolled in the SCOOP study were assessed in comparison with the adult reference population simulated using the GARNET population PK model (500 mg Q3W). Pediatric concentrations were evaluated alongside adult simulations at 1 h, 168 h, and 504 h post-dose. At 1 h, concentrations across pediatric cohorts (1A, 1B, osteosarcoma expansion, and neuroblastoma expansion) ranged from 124.7 to 186 ng/mL, while the simulated adult value was 159.6 ng/mL. At 168 h, pediatric values ranged from 55.6 to 91.8 ng/mL compared with 68.4 ng/mL in adults. At 504 h, concentrations in pediatric cohorts ranged from 35.1 to 45.7 ng/mL, and the corresponding adult simulation was 40.4 ng/mL.

Overall, across all evaluated timepoints, pediatric concentration ranges were within or close to the adult prediction interval, supporting comparable exposure between pediatric subjects and adults receiving the 500 mg Q3W regimen.

Issue is considered resolved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance