Clinical trial results:
ESP1/SARC025 Global Collaboration: A Phase I Study of a Combination of the PARP inhibitor, Niraparib and Temozolomide and/or Irinotecan in Patients with Previously Treated, incurable Ewing Sarcoma

Summary

EudraCT number	2014-005541-50
Trial protocol	GB FR
Global end of trial date	30 November 2020

Results information

Result version number	v1 (current)
This version publication date	12 June 2021
First version publication date	12 June 2021

Trial information

Trial identification

Sponsor protocol code	ESP1/SARC025

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02044120
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sarcoma Alliance for Research through Collaboration (SARC)
Sponsor organisation address	PO Box 406, Ann Arbor, United States, MI 48106
Public contact	Dr Sandra Strauss, University College London Hospital NHS Foundation Trust, +44 2034479358, s.strauss@ucl.ac.uk
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2020
Global end of trial reached?	Yes
Global end of trial date	30 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the study is to find the optimal dose of a combination of niraparib and temozolomide or irinotecan or irinotecan and temozolomide that can safely be given to patients with relapsed Ewing sarcoma (the maximum tolerated dose) and what side effects limit the doses we can give (dose limiting toxicities).

Protection of trial subjects:

The study has been conducted in accordance with GCP as specified in ICH E6, and the guiding principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	34
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	4
Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Assessments and procedures were conducted within 28 days prior to first dose of study treatment and included study eligibility (inclusion/exclusion criteria), signed informed consent, biopsy of tumor and tumor assessment (CT or MRI scans of known disease sites).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm 1 - Niraparib and Temozolomide

Arm description:

Niraparib (capsule) and temozolomide(capsule) taken together.

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Eligible patients in Arm 1 received continuous Niraparib daily and escalating Temozolomide (days 2-6 [D2-6]) in cohort A. Subsequent patients received intermittent Niraparib dosing (cohort B), with Temozolomide re-escalation in cohort C.

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Eligible patients in Arm 1 received continuous Niraparib daily and escalating Temozolomide (days 2-6 [D2-6]) in cohort A. Subsequent patients received intermittent Niraparib dosing (cohort B), with Temozolomide re-escalation in cohort C.

Arm title	Arm 2 - Niraparib and Irinotecan

Arm description:

Niraparib taken orally and Irinotecan administered intravenously.

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In Arm 2, patients were treated with doses of Niraparib 100 mg to 300 mg (days 1-7 [D1-7]) and escalating doses of Irinotecan 20 mg/m2 to 50 mg/m2 (D2-6) of a 28-day cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

In Arm 2, patients were treated with doses of Niraparib 100 mg to 300 mg (days 1-7 [D1-7]) and escalating doses of Irinotecan 20 mg/m2 to 50 mg/m2 (D2-6) of a 28-day cycle.

Arm title	Arm 3 - Niraparib, Irinotecan and Temozolomide

Arm description:

Niraparib and temozolomide taken orally. Irinotecan administered intravenously.

Arm type	Experimental
Investigational medicinal product name	Niraparib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In Arm 3, patients were treated with Niraparib 100 mg d1-7, Irinotecan 20 mg/m2 d2-6 and Temozolomide 15mg/m2 -25mg/m2 d2-6 of a 28-day cycle.

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

In Arm 3, patients were treated with Niraparib 100 mg d1-7, Irinotecan 20 mg/m2 d2-6 and Temozolomide 15mg/m2 -25mg/m2 d2-6 of a 28-day cycle.

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

In Arm 3, patients were treated with Niraparib 100 mg d1-7, Irinotecan 20 mg/m2 d2-6 and Temozolomide 15mg/m2 -25mg/m2 d2-6 of a 28-day cycle.

Number of subjects in period 1	Arm 1 - Niraparib and Temozolomide	Arm 2 - Niraparib and Irinotecan	Arm 3 - Niraparib, Irinotecan and Temozolomide
Started	17	12	5
Completed	17	12	5

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1 - Niraparib and Temozolomide
Reporting group description: Niraparib (capsule) and temozolomide(capsule) taken together.	
Reporting group title	Arm 2 - Niraparib and Irinotecan
Reporting group description: Niraparib taken orally and Irinotecan administered intravenously.	
Reporting group title	Arm 3 - Niraparib, Irinotecan and Temozolomide
Reporting group description: Niraparib and temozolomide taken orally. Irinotecan administered intravenously.	

Reporting group values	Arm 1 - Niraparib and Temozolomide	Arm 2 - Niraparib and Irinotecan	Arm 3 - Niraparib, Irinotecan and Temozolomide
Number of subjects	17	12	5
Age categorical Units: Subjects			
Adolescents (12-17 years)	2	2	0
Adults (18-64 years)	15	10	5
Gender categorical Units: Subjects			
Female	3	3	2
Male	14	9	3

Reporting group values	Total		
Number of subjects	34		
Age categorical Units: Subjects			
Adolescents (12-17 years)	4		
Adults (18-64 years)	30		
Gender categorical Units: Subjects			
Female	8		
Male	26		

End points

End points reporting groups

Reporting group title	Arm 1 - Niraparib and Temozolomide
Reporting group description:	
Niraparib (capsule) and temozolomide(capsule) taken together.	
Reporting group title	Arm 2 - Niraparib and Irinotecan
Reporting group description:	
Niraparib taken orally and Irinotecan administered intravenously.	
Reporting group title	Arm 3 - Niraparib, Irinotecan and Temozolomide
Reporting group description:	
Niraparib and temozolomide taken orally. Irinotecan administered intravenously.	

Primary: Dose-limiting Toxicity and Maximum Tolerated Dose

End point title	Dose-limiting Toxicity and Maximum Tolerated Dose[1]
End point description:	
Dose limiting toxicity describes side effects of a drug or other treatment that are serious enough to prevent an increase in dose or level of that treatment. The maximum tolerated dose is the highest dose of a drug or treatment that does not cause unacceptable side effects. The MTD is Niraparib 200mg qd D1-7 plus Temozolomide 30mg/m2 qd on D2-6 (Arm 1) and Niraparib 100mg qd D1-7 plus Irinotecan 20mg/m2 qd D2-6 (Arm 2). The MTD for Arm 3 was not reached.	
End point type	Primary
End point timeframe:	
Approximately 24 months	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Arm 1 Cohort A utilized a continual reassessment method (CRM) design to determine the MTD of TMZ in combination with niraparib in patients with pre-treated incurable Ewing Sarcoma. Arm 1, Cohorts B and C, Arm 2 and Arm 3 utilized the traditional 3+3 dose escalation design.	

End point values	Arm 1 - Niraparib and Temozolomide	Arm 2 - Niraparib and Irinotecan	Arm 3 - Niraparib, Irinotecan and Temozolomide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	12	5	
Units: Number of patients who experienced DLT	5	3	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Tumor Response Rate

End point title	Tumor Response Rate
End point description:	
Number of patients with partial response, progressive disease, or stable disease as best tumor response. One partial response was found in Arm 2, and the duration of response was 84 days. Non-evaluable patients did not have follow-up scans before coming off the study.	

End point type	Secondary
End point timeframe: Approximately 24 months	

End point values	Arm 1 - Niraparib and Temozolomide	Arm 2 - Niraparib and Irinotecan	Arm 3 - Niraparib, Irinotecan and Temozolomide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	12	5	
Units: Number of patients				
Partial Response	0	1	0	
Progressive Disease	12	5	5	
Stable Disease	2	6	0	
Non-evaluable	3	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival
End point description: Progression-free survival at months 4 and 6	
End point type	Secondary
End point timeframe: Months 4 and 6	

End point values	Arm 1 - Niraparib and Temozolomide	Arm 2 - Niraparib and Irinotecan	Arm 3 - Niraparib, Irinotecan and Temozolomide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	12	5	
Units: Number of patients				
Progression before month 4	17	7	3	
No progression before month 4	0	5	2	
Progression before month 6	17	10	4	
No progression before month 6	0	2	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

The time from tumor response to disease progression.

End point type	Secondary

End point timeframe:

Approximately 24 months

End point values	Arm 1 - Niraparib and Temozolomide	Arm 2 - Niraparib and Irinotecan	Arm 3 - Niraparib, Irinotecan and Temozolomide	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	12	5	
Units: Number of patients				
Patients alive at the end of the study	15	10	4	
Mortality	2	2	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs: from the day of the signed ICF until 30 days after last dose of study treatment.
SAEs and AESIs: from the day of signed ICF until 90 days after the last dose of study drug (or until start of alternate anticancer therapy, whichever occurred first).

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	Niraparib and Temozolomide

Reporting group description:

Niraparib (capsule) and temozolomide (capsule) will be taken together.
niraparib
Temozolomide

Reporting group title	Niraparib and Irinotecan

Reporting group description:

Niraparib will be taken orally and irinotecan will be administered intravenously.
niraparib
Irinotecan

Reporting group title	Niraparib, Irinotecan and Temozolomide

Reporting group description:

Niraparib and temozolomide will be taken orally. Irinotecan will be administered intravenously.
niraparib
Temozolomide
Irinotecan

Serious adverse events	Niraparib and Temozolomide	Niraparib and Irinotecan	Niraparib, Irinotecan and Temozolomide
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 17 (41.18%)	4 / 12 (33.33%)	2 / 5 (40.00%)
number of deaths (all causes)	2	2	1
number of deaths resulting from adverse events			
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	3 / 17 (17.65%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death NOS	Additional description: Death that cannot be attributed to a CTCAE term associated with Grade 5.		
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fever			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General Disorders and Administration Site Conditions - Other			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	0 / 17 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Joint infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			

subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Niraparib and Temozolomide	Niraparib and Irinotecan	Niraparib, Irinotecan and Temozolomide
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)	12 / 12 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	1	1	4
Hypotension			
subjects affected / exposed	3 / 17 (17.65%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	7	5	2
Thromboembolic Event			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Gastrointestinal Disorders - Other			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Edema Limbs			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Edema Trunk			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Facial pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	8 / 17 (47.06%)	6 / 12 (50.00%)	2 / 5 (40.00%)
occurrences (all)	8	14	2

Fever			
subjects affected / exposed	3 / 17 (17.65%)	3 / 12 (25.00%)	2 / 5 (40.00%)
occurrences (all)	6	7	4
General Disorders and Administration Site Conditions - Other			
subjects affected / exposed	0 / 17 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	5	0
Pain			
subjects affected / exposed	3 / 17 (17.65%)	1 / 12 (8.33%)	3 / 5 (60.00%)
occurrences (all)	3	1	3
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Allergic rhinitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 17 (17.65%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	4	2	0
Dyspnea			
subjects affected / exposed	2 / 17 (11.76%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	4	3	1
Epistaxis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pneumothorax			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Productive cough			

subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Respiratory, Thoracic and Mediastinal Disorders - Other			
subjects affected / exposed	2 / 17 (11.76%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Sneezing			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sore throat			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Wheezing			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 17 (11.76%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Insomnia			
subjects affected / exposed	5 / 17 (29.41%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	5	1	0
Psychiatric Disorders - Other			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	6 / 17 (35.29%)	2 / 12 (16.67%)	1 / 5 (20.00%)
occurrences (all)	10	5	1
Alkaline Phosphatase Increased			
subjects affected / exposed	8 / 17 (47.06%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	12	0	0
Aspartate aminotransferase increased			

subjects affected / exposed	5 / 17 (29.41%)	1 / 12 (8.33%)	2 / 5 (40.00%)
occurrences (all)	7	2	2
Creatinine Increased			
subjects affected / exposed	5 / 17 (29.41%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	9	3	5
Electrocardiogram QT Corrected Interval Prolonged			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
INR Increased	Additional description: INR = International Normalized Ratio		
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Investigations - Other			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Lymphocyte count decreased			
subjects affected / exposed	6 / 17 (35.29%)	3 / 12 (25.00%)	2 / 5 (40.00%)
occurrences (all)	20	6	9
Neutrophil count decreased			
subjects affected / exposed	6 / 17 (35.29%)	5 / 12 (41.67%)	2 / 5 (40.00%)
occurrences (all)	25	6	9
Platelet count decreased			
subjects affected / exposed	13 / 17 (76.47%)	4 / 12 (33.33%)	2 / 5 (40.00%)
occurrences (all)	30	4	3
Weight Loss			
subjects affected / exposed	4 / 17 (23.53%)	1 / 12 (8.33%)	2 / 5 (40.00%)
occurrences (all)	5	1	2
White Blood Cell Decreased			
subjects affected / exposed	9 / 17 (52.94%)	4 / 12 (33.33%)	2 / 5 (40.00%)
occurrences (all)	34	9	6
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Fall			

subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Injury, Poisoning and Procedural Complications - Other			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac Disorders - Other			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sinus tachycardia			
subjects affected / exposed	3 / 17 (17.65%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	6	8	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	4	0
Dysgeusia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Headache			
subjects affected / exposed	3 / 17 (17.65%)	2 / 12 (16.67%)	1 / 5 (20.00%)
occurrences (all)	3	2	3
Nervous System Disorders - Other			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Paresthesia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Trigeminal nerve disorder			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Anemia			
subjects affected / exposed	10 / 17 (58.82%)	5 / 12 (41.67%)	2 / 5 (40.00%)
occurrences (all)	28	8	8
Blood and Lymphatic System Disorders - Other			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Ear and labyrinth disorders			
Ear and Labyrinth Disorders - Other			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Blurred vision			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Eye disorders - Other			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 17 (17.65%)	6 / 12 (50.00%)	0 / 5 (0.00%)
occurrences (all)	4	11	0
Bloating			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Colitis			
subjects affected / exposed	0 / 17 (0.00%)	3 / 12 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Constipation			
subjects affected / exposed	5 / 17 (29.41%)	3 / 12 (25.00%)	0 / 5 (0.00%)
occurrences (all)	6	4	0
Diarrhoea			
subjects affected / exposed	3 / 17 (17.65%)	10 / 12 (83.33%)	5 / 5 (100.00%)
occurrences (all)	4	35	10

Dyspepsia			
subjects affected / exposed	2 / 17 (11.76%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Muscositis Oral			
subjects affected / exposed	0 / 17 (0.00%)	3 / 12 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	12 / 17 (70.59%)	12 / 12 (100.00%)	5 / 5 (100.00%)
occurrences (all)	25	23	13
Rectal Hemorrhage			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	9 / 17 (52.94%)	7 / 12 (58.33%)	4 / 5 (80.00%)
occurrences (all)	23	9	13
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rash maculo-papular			
subjects affected / exposed	3 / 17 (17.65%)	1 / 12 (8.33%)	1 / 5 (20.00%)
occurrences (all)	3	1	1
Skin and Subcutaneous Tissue Disorders - Other			
subjects affected / exposed	0 / 17 (0.00%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			

Proteinuria			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Renal and Urinary Disorders - Other			
subjects affected / exposed	2 / 17 (11.76%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	2
Chest wall pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and Connective Tissue Disorder - Other			
subjects affected / exposed	5 / 17 (29.41%)	2 / 12 (16.67%)	1 / 5 (20.00%)
occurrences (all)	10	2	1
Myalgia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	2 / 17 (11.76%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Infections and infestations			
Infections and Infestations - Other			
subjects affected / exposed	2 / 17 (11.76%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	3	2	0
Lung Infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rhinitis Infective			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Sinusitis			

subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Urinary tract infection			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	4 / 17 (23.53%)	6 / 12 (50.00%)	1 / 5 (20.00%)
occurrences (all)	6	8	1
Dehydration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hyperglycemia			
subjects affected / exposed	4 / 17 (23.53%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	10	2	0
Hypernatraemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hypoalbuminaemia			
subjects affected / exposed	5 / 17 (29.41%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	10	0	2
Hypocalcemia			
subjects affected / exposed	2 / 17 (11.76%)	1 / 12 (8.33%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Hypomagnesaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	4 / 17 (23.53%)	0 / 12 (0.00%)	3 / 5 (60.00%)
occurrences (all)	6	0	3

Hypophosphataemia			
subjects affected / exposed	1 / 17 (5.88%)	2 / 12 (16.67%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Metabolism and Nutrition Disorders - Other			
subjects affected / exposed	1 / 17 (5.88%)	0 / 12 (0.00%)	2 / 5 (40.00%)
occurrences (all)	2	0	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2014	The protocol ESP1/SARC025 was updated from the original version 1 dated 12 November 2013 to version 1.1 dated 03 January 2014. The substantial changes included the modification of the secondary objectives and eligibility criteria.
12 September 2014	The protocol ESP1/SARC025 was updated from version 1.1 dated 03 January 2014 to version 2 dated 12 September 2014. The substantial changes included the addition of a secondary objective to evaluate candidate metastasis-associated genes and proteins in collected tumor samples to better understand Ewing's sarcoma biology and explain rationale for studies chosen, the addition of additional cohorts of patients to potentially evaluate lower doses of niraparib based on high incidence of myelosuppression seen in early patients treated on study, the adjustment to the dose modification guidelines based on emerging data from ongoing studies of single agent niraparib and the clarification of logistical issues in patient schedule and data/regulatory management.
26 October 2015	The protocol ESP1/SARC025 was updated from version 2 dated 12 September 2014 to version 3 dated 26 October 2015. The substantial changes concerned the addition of another arm to the study investigating the combination of niraparib and irinotecan and additional safety monitoring for patients treated with niraparib in light of new safety information that had been received.
12 September 2018	The protocol ESP1/SARC025 was updated from version 3 dated 26 October 2015 to version 4 dated 12 September 2018. The substantial changes made to the protocol were the addition of a new treatment arm: Arm 3 Niraparib plus Irinotecan plus Temozolomide, the addition of new data relating to toxicity and SEAs, revisions to inclusion/exclusion criteria relating to pregnancy testing and AML, new sections on Adverse Events of Special Interest and Special Situations (Abuse, Misuse, Medication Errors, Overdose, and Accidental or Occupational Exposure), and changes in tumour biopsies schedule.
16 October 2020	The protocol ESP1/SARC025 was updated from version 4 dated 12 September 2018 to version 5 dated 16 October 2020. This protocol version incorporated language consistent with the updated niraparib Investigator's Brochure (version 11), revised text from "Tesaro" to "GSK" and incorporated GSK-specific language.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The trial was approved in France but never started; the French competent authority and ethics committee approvals subsequently expired.

Notes: