



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 |
| Scientific contact | Dr Sandra Strauss, University College London Hospital NHS Foundation Trust, +44 2034479358, s.strauss@ucl.ac.uk |

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/m ² qd on D2-6 (Arm 1) and Niraparib 100mg qd D1-7 plus Irinotecan 20mg/m ² 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 occurrences (all) | 0 / 17 (0.00%) 0 | 0 / 12 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Injury, Poisoning and Procedural Complications - Other subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Cardiac disorders Cardiac Disorders - Other subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 6 | 1 / 12 (8.33%) 8 | 1 / 5 (20.00%) 1 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 12 (16.67%) 4 | 0 / 5 (0.00%) 0 |
| Dysgeusia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 2 / 12 (16.67%) 2 | 0 / 5 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 3 / 17 (17.65%) 3 | 2 / 12 (16.67%) 2 | 1 / 5 (20.00%) 3 |
| Nervous System Disorders - Other subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 1 / 12 (8.33%) 2 | 0 / 5 (0.00%) 0 |
| Paresthesia subjects affected / exposed occurrences (all) | 1 / 17 (5.88%) 1 | 0 / 12 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Trigeminal nerve disorder subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 |
| Neuralgia subjects affected / exposed occurrences (all) | 0 / 17 (0.00%) 0 | 1 / 12 (8.33%) 1 | 0 / 5 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |

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

| | | | |
|--|------------------|-------------------|-----------------|
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 17 (11.76%) | 0 / 12 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Mucositis 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 "Tesar" 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: