



Clinical trial results:

Window study of the PARP inhibitor rucaparib in patients with primary triple negative or BRCA1/2 related breast cancer (RIO)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-003319-12 |
| Trial protocol | GB |
| Global end of trial date | 04 June 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 June 2020 |
| First version publication date | 20 June 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------------------|
| Sponsor protocol code | ICR-CTSU-2014-10046 |
|-----------------------|---------------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | ISRCTN92154110 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Sponsor Identification Number: CCR4109, ICR-CTSU Protocol number: ICR-CTSU/2014/10046, CRUK Reference Number: CRUK/12/034, Main REC Reference: 14/LO/2181, MHRA CTA Reference Number: 15983/0255/001-0001 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | The Institute of Cancer Research:Royal Cancer Hospital |
| Sponsor organisation address | 123 Old Brompton Road, London, United Kingdom, SW7 3RP |
| Public contact | Christy Toms, The Institute of Cancer Research, +44 02087224266, rio-icrctsu@icr.ac.uk |
| Scientific contact | Christy Toms, The Institute of Cancer Research, +44 02087224266, rio-icrctsu@icr.ac.uk |
| Sponsor organisation name | The Royal Marsden NHS Foundation Trust |
| Sponsor organisation address | Fulham Road, London, United Kingdom, SW3 6JJ |
| Public contact | Christy Toms, The Royal Marsden Foundation Trust, +44 02087224266, rio-icrctsu@icr.ac.uk |
| Scientific contact | Christy Toms, The Royal Marsden NHS Foundation Trust, +44 0207224266, rio-icrctsu@icr.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 | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 July 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 23 April 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 June 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main aim of the study was to determine the proportion of triple negative breast cancers (TNBCs) that respond to 12-14 days treatment with the PARP inhibitor rucaparib. The cell proliferation marker Ki67 will be used to measure treatment response.

Ki67 has been widely used to measure proliferation in human breast cancer. Preclinical studies have shown that Ki67 levels decrease in response to PARP inhibition in xenografts of an HR deficient cancer cell line and that the degree of suppression of Ki67 is also associated with the magnitude of xenograft response to PARP inhibition in vivo.

The exploratory analysis of Ki67 in BRCA1 and BRCA2 germline mutation carriers will be used to assess the validity of fall in Ki67 as a surrogate for sensitivity to rucaparib. From prior work it is anticipated that a majority of untreated BRCA1 and BRCA2 related cancers should show a fall in Ki67 on rucaparib.

Protection of trial subjects:

Patients were provided with full verbal and written informed consent regarding the purpose and procedures of the trial and the possible risks involved. A patient information sheet and consent form were provided and patients were given sufficient time to consider their participation. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.

Core biopsies were a mandatory aspect of trial participation, the scientific value of these samples were considered a very important aspect of the trial when evaluated during the formal peer review process. The procedures and reasons for sample collection were clearly described in the patient information sheet and every effort to minimise discomfort during the biopsy procedure was taken by qualified healthcare professionals.

Full details of the trial medication and its safety profile were provided in the patient information sheet. Patients had the opportunity to discuss any concerns they had in relation to this with their study team at site.

Background therapy:

The purpose of RIO was to establish the proportion of untreated patients with primary sporadic TNBC who demonstrated sensitivity to the PARP inhibitor rucaparib. The trial therefore utilised a 'window of opportunity' design to allow assessment of rucaparib within the window between diagnosis and scheduling of standard treatment.

Evidence for comparator:

This was a single group, open label phase II trial. All patients in the trial received 12-14 days of rucaparib treatment.

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 43 |
| Worldwide total number of subjects | 43 |
| EEA total number of subjects | 43 |

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) | 0 |
| Adults (18-64 years) | 31 |
| From 65 to 84 years | 11 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Forty three patients were recruited from eight UK centers between July 2015 and October 2017.

Pre-assignment

Screening details:

Patients diagnosed with triple negative breast cancer or BRCA1/2-related breast cancer meeting the RIO eligibility criteria were recruited into the study.

Period 1

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

Arms

| | |
|------------------|-----------|
| Arm title | Rucaparib |
|------------------|-----------|

Arm description:

Trial treatment consisting of 12-14 days of rucaparib prior to surgery of neoadjuvant chemotherapy.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | rucaparib |
| Investigational medicinal product code | CO-338 |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Rucaparib was provided as 120mg tablets and taken at a dose of 600mg twice daily for 12-14 days

| Number of subjects in period 1 | Rucaparib |
|--|-----------|
| Started | 43 |
| Commenced treatment | 42 |
| Completed | 31 |
| Not completed | 12 |
| Did not start treatment (patient choice) | 1 |
| Discontinued early for sufficient washout (AE) | 1 |
| Discontinued early due to other reasons | 2 |
| Adverse event, non-fatal | 7 |
| Interruption due to patient error | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|---------------|
| Reporting group title | Overall Trial |
| Reporting group description: - | |

| Reporting group values | Overall Trial | Total | |
|------------------------|---------------|-------|--|
| Number of subjects | 43 | 43 | |
| Age categorical | | | |
| Units: Subjects | | | |
| <40 | 7 | 7 | |
| 40-49 | 13 | 13 | |
| 50-59 | 9 | 9 | |
| 60-69 | 5 | 5 | |
| 70+ | 9 | 9 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.6 | | |
| standard deviation | ± 13.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 43 | 43 | |
| Male | 0 | 0 | |

Subject analysis sets

| | |
|----------------------------|-------------------------------------|
| Subject analysis set title | Intention to Treat population (ITT) |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

This population contains all people registered into the study (regardless of whether they were later found to be ineligible, a protocol deviator, never treated etc.)

| | |
|----------------------------|-----------------------------|
| Subject analysis set title | As treated population (ATP) |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

This population contains all patients who received at least one dose of rucaparib

| | |
|----------------------------|----------------------------|
| Subject analysis set title | Biological population (BP) |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All sporadic triple negative patients who have been registered and have a measurement for the biomarker in question (for the relevant endpoint) both at baseline and at the end of rucaparib treatment (surgery/end of treatment biopsy - only collected if the patient received ≥ 7 days of rucaparib). Patients who are found to have a BRCA mutation after trial entry will be included in this population but those entered as known BRCA mutation carriers will be excluded.

| Reporting group values | Intention to Treat population (ITT) | As treated population (ATP) | Biological population (BP) |
|------------------------|-------------------------------------|-----------------------------|----------------------------|
| Number of subjects | 43 | 42 | 25 |
| Age categorical | | | |
| Units: Subjects | | | |
| <40 | 7 | 7 | 4 |
| 40-49 | 13 | 12 | 6 |

| | | | |
|--------------------|--------|--------|--------|
| 50-59 | 9 | 9 | 6 |
| 60-69 | 5 | 5 | 3 |
| 70+ | 9 | 9 | 6 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 54.6 | 54.9 | 55.5 |
| standard deviation | ± 13.9 | ± 13.9 | ± 13.9 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 43 | 42 | 25 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Rucaparib |
| Reporting group description: Trial treatment consisting of 12-14 days of rucaparib prior to surgery of neoadjuvant chemotherapy. | |
| Subject analysis set title | Intention to Treat population (ITT) |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: This population contains all people registered into the study (regardless of whether they were later found to be ineligible, a protocol deviator, never treated etc.) | |
| Subject analysis set title | As treated population (ATP) |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: This population contains all patients who received at least one dose of rucaparib | |
| Subject analysis set title | Biological population (BP) |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All sporadic triple negative patients who have been registered and have a measurement for the biomarker in question (for the relevant endpoint) both at baseline and at the end of rucaparib treatment (surgery/end of treatment biopsy - only collected if the patient received ≥ 7 days of rucaparib). Patients who are found to have a BRCA mutation after trial entry will be included in this population but those entered as known BRCA mutation carriers will be excluded. | |

Primary: Ki67 response

| | |
|--|------------------------------|
| End point title | Ki67 response ^[1] |
| End point description: Ki67 response from trial entry to end of rucaparib treatment is assessed in patients with sporadic triple negative cancers (biological population). Response to rucaparib is defined as 50% or greater fall in Ki67 from baseline. | |
| End point type | Primary |
| End point timeframe: From trial entry to the end of 12-14 days rucaparib treatment. | |

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: This is a single arm study and no comparative analysis was performed, however the system expects at least 2 groups to be identified. All methods and options specified in the analysis section apply to statistical methods and summary measures to report and compare at least 2 independent groups, which is not the case in this single arm trial. There is no way of reporting one group inference and summary values without triggering an error or reporting inaccurate information.

| End point values | Rucaparib | Biological population (BP) | | |
|-----------------------------|-----------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 25 | 25 | | |
| Units: Patients | | | | |
| Responder | 3 | 3 | | |
| Non-responder | 22 | 22 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Apoptosis induction

| | |
|-----------------|---------------------|
| End point title | Apoptosis induction |
|-----------------|---------------------|

End point description:

The proportion of sporadic TNBC patients who have any increase in apoptosis after 12-14 days of rucaparib treatment will be presented. This will be assessed on the biological population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From trial entry to the end of 12-14 days of rucaparib treatment.

| End point values | Rucaparib | Biological population (BP) | | |
|-----------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 23 ^[2] | 23 ^[3] | | |
| Units: Patients | | | | |
| Apoptosis induction | 13 | 13 | | |
| No apoptosis induction | 10 | 10 | | |

Notes:

[2] - Samples from 2 patients in the biological population were non evaluable for apoptosis induction.

[3] - Samples from 2 patients in the biological population were non evaluable for apoptosis induction.

Statistical analyses

No statistical analyses for this end point

Secondary: Association between sporadic TNBC and evidence of a defect in HR based DNA repair

| | |
|-----------------|---|
| End point title | Association between sporadic TNBC and evidence of a defect in HR based DNA repair |
|-----------------|---|

End point description:

The proportion of patients with low RAD51 will be presented. RAD51 low is classed as RAD51 foci<20 on the end of treatment biopsy.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From trial entry to end of 12-14 days rucaparib treatment

| End point values | Rucaparib | Biological population (BP) | | |
|-----------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 21 ^[4] | 21 ^[5] | | |
| Units: Patients | | | | |
| RAD51 low | 16 | 16 | | |
| RAD51 high | 5 | 5 | | |

Notes:

[4] - Samples from 4 patients in the biological population were non-evaluable for RAD51 assessment.

[5] - Samples from 4 patients in the biological population were non-evaluable for RAD51 assessment.

Statistical analyses

No statistical analyses for this end point

Secondary: Association between percentage change in apoptosis with ki67 response

| | |
|-----------------|---|
| End point title | Association between percentage change in apoptosis with ki67 response |
|-----------------|---|

End point description:

Association is assessed via logistic regression with Ki67 response yes/no (defined as a 50% decrease in Ki67) as the outcome and percentage change apoptosis as the explanatory variable. Odds ratios are unadjusted for other variables.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From trial entry to end of 12-14 days rucaparib treatment.

| End point values | Rucaparib | Biological population (BP) | | |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 23 ^[6] | 23 ^[7] | | |
| Units: Odds ratio | | | | |
| number (confidence interval 95%) | 0.97 (0.92 to 1.02) | 0.97 (0.92 to 1.02) | | |

Notes:

[6] - Samples from 2 patients in the biological population were non-evaluable for apoptosis.

[7] - Samples from 2 patients in the biological population were non-evaluable for apoptosis.

Statistical analyses

No statistical analyses for this end point

Secondary: Association between RAD51 score and ki67 response

| | |
|-----------------|---|
| End point title | Association between RAD51 score and ki67 response |
|-----------------|---|

End point description:

Association is assessed via logistic regression with Ki67 response yes/no (defined as a 50% decrease in Ki67) as the outcome and continuous RAD51 score measured on the end of treatment biopsy as the explanatory variable. Odds ratios are unadjusted for other variables.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From trial entry to end of 12-14 days rucaparib treatment.

| End point values | Rucaparib | Biological population (BP) | | |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 19 ^[8] | 19 ^[9] | | |
| Units: Odds ratio | | | | |
| number (confidence interval 95%) | 0.88 (0.58 to 1.34) | 0.88 (0.58 to 1.34) | | |

Notes:

[8] - Samples from 6 patients in the biological population were non-evaluable for RAD51

[9] - Samples from 6 patients in the biological population were non-evaluable for RAD51

Statistical analyses

No statistical analyses for this end point

Secondary: Association between BRCA1 methylation and Ki67 response

| | |
|-----------------|---|
| End point title | Association between BRCA1 methylation and Ki67 response |
|-----------------|---|

End point description:

Association is assessed via logistic regression with Ki67 response yes/no (defined as a 50% decrease in Ki67) as the outcome and BRCA1 methylation status (methylated vs. non-methylated) as the explanatory variable. Odds ratios are unadjusted for other variables.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From trial entry to end of 12-14 days rucaparib treatment

| End point values | Rucaparib | Biological population (BP) | | |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 25 | 25 | | |
| Units: Odds ratio | | | | |
| number (confidence interval 95%) | 0.32 (0.02 to 4.66) | 0.32 (0.02 to 4.66) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Association of percentage change in apoptosis with RAD51

| | |
|-----------------|--|
| End point title | Association of percentage change in apoptosis with RAD51 |
|-----------------|--|

End point description:

Association is assessed via logistic regression with RAD51 high/low (using cut-off of 20) as the outcome and percentage change apoptosis as the explanatory variable. Odds ratios are unadjusted for other variables.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From trial entry to end of 12-14 days rucaparib treatment

| End point values | Rucaparib | Biological population (BP) | | |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 18 ^[10] | 18 ^[11] | | |
| Units: Odds ratio | | | | |
| number (confidence interval 95%) | 0.99 (0.97 to 1.01) | 0.99 (0.97 to 1.01) | | |

Notes:

[10] - Samples from 7 patients in the biological population were non-evaluable for RAD51 and/or apoptosis

[11] - Samples from 7 patients in the biological population were non-evaluable for RAD51 and/or apoptosis

Statistical analyses

No statistical analyses for this end point

Other pre-specified: To explore change in circulating tumour DNA levels between baseline and day 12-14 as a surrogate for efficacy of rucaparib

| | |
|-----------------|--|
| End point title | To explore change in circulating tumour DNA levels between baseline and day 12-14 as a surrogate for efficacy of rucaparib |
|-----------------|--|

End point description:

ctDNA day12-14 to baseline ratio was compared between BRCA1/2 mutant and BRCA1/2 wildtype tumours. Patients with germline BRCA1/2 mutations had greater suppression than wildtype samples.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

From trial entry to end of 12-14 days rucaparib treatment

| End point values | Rucaparib | As treated population (ATP) | | |
|--------------------------------------|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 19 ^[12] | 19 ^[13] | | |
| Units: p-value for Mann-Whitney test | | | | |
| number (not applicable) | 0.021 | 0.021 | | |

Notes:

[12] - 19 patients had paired ctDNA samples evaluable

[13] - 19 patients had paired ctDNA samples evaluable

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Association between change in ctDNA and RAD51 foci formation

| | |
|-----------------|--|
| End point title | Association between change in ctDNA and RAD51 foci formation |
|-----------------|--|

End point description:

Change in ctDNA was compared between tumours deficient and normal RAD51 foci formation. Cancers with deficient RAD51 foci formation had greater ctDNA suppression.

| | |
|---|---------------------|
| End point type | Other pre-specified |
| End point timeframe: | |
| From trial entry to end of 12-14 days rucaparib treatment | |

| End point values | Rucaparib | As treated population (ATP) | | |
|---------------------------------------|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 12 ^[14] | 12 ^[15] | | |
| Units: p-value from Mann-Whitney test | | | | |
| number (not applicable) | 0.033 | 0.033 | | |

Notes:

[14] - 12 patients had samples evaluable for RAD51 and ctDNA change

[15] - 12 patients had samples evaluable for RAD51 and ctDNA change

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Association between change in ctDNA and HRDetect status

| | |
|---|---|
| End point title | Association between change in ctDNA and HRDetect status |
| End point description: | |
| Change in ctDNA was compared between HRDetect positive and negative tumours. HRDetect positive cancers had greater ctDNA suppression. | |
| End point type | Other pre-specified |
| End point timeframe: | |
| From trial entry to end of 12-14 days rucaparib treatment. | |

| End point values | Rucaparib | As treated population (ATP) | | |
|---------------------------------------|--------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 15 ^[16] | 15 ^[17] | | |
| Units: p-value from Mann-Whitney test | | | | |
| number (not applicable) | 0.027 | 0.027 | | |

Notes:

[16] - 15 patients had samples evaluable for HRDetect and ctDNA change

[17] - 15 patients had samples evaluable for HRDetect and ctDNA change

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported up to 28 days post-rucaparib treatment

Adverse event reporting additional description:

Adverse events of any grade were reported from trial entry until 28 days post-rucaparib treatment. Adverse event data is reported for patients who received at least one dose of rucaparib. In the non-serious adverse event section we report all events reported at any grade in at least 5% of patients.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Rucaparib |
|-----------------------|-----------|

Reporting group description:

Trial treatment consisting of 12-14 days of rucaparib prior to surgery of neoadjuvant chemotherapy.

| Serious adverse events | Rucaparib | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 42 (9.52%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Delayed recovery from anaesthesia | | | |
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 42 (4.76%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 42 (2.38%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 0.05 %

| Non-serious adverse events | Rucaparib | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 42 / 42 (100.00%) | | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Hypertension | | | |
| subjects affected / exposed | 23 / 42 (54.76%) | | |
| occurrences (all) | 50 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 42 (11.90%) | | |
| occurrences (all) | 6 | | |
| Fatigue | | | |
| subjects affected / exposed | 30 / 42 (71.43%) | | |
| occurrences (all) | 59 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Reproductive system and breast disorders | | | |
| Breast pain | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 5 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Psychiatric disorders | | | |

| | | | |
|---|------------------------|--|--|
| Anxiety subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 5 | | |
| Insomnia subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 6 | | |
| Investigations Adjusted calcium subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 10 | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 7 / 42 (16.67%) 8 | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 9 / 42 (21.43%) 12 | | |
| Haemoglobin increased subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 4 | | |
| Liver function test increased subjects affected / exposed occurrences (all) | 29 / 42 (69.05%) 36 | | |
| Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all) | 3 / 42 (7.14%) 3 | | |
| Cardiac disorders Tachycardia subjects affected / exposed occurrences (all) | 5 / 42 (11.90%) 5 | | |
| Nervous system disorders Dizziness | | | |

| | | | |
|--------------------------------------|------------------|--|--|
| subjects affected / exposed | 11 / 42 (26.19%) | | |
| occurrences (all) | 20 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 10 / 42 (23.81%) | | |
| occurrences (all) | 14 | | |
| Headache | | | |
| subjects affected / exposed | 19 / 42 (45.24%) | | |
| occurrences (all) | 35 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | | |
| occurrences (all) | 10 | | |
| Leukopenia | | | |
| subjects affected / exposed | 7 / 42 (16.67%) | | |
| occurrences (all) | 8 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 12 / 42 (28.57%) | | |
| occurrences (all) | 20 | | |
| Neutropenia | | | |
| subjects affected / exposed | 6 / 42 (14.29%) | | |
| occurrences (all) | 7 | | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 3 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 42 (7.14%) | | |
| occurrences (all) | 4 | | |
| Constipation | | | |
| subjects affected / exposed | 12 / 42 (28.57%) | | |
| occurrences (all) | 18 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 42 (28.57%) | | |
| occurrences (all) | 14 | | |
| Dyspepsia | | | |

| | | | |
|---|---|--|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Flatulence</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>13 / 42 (30.95%)</p> <p>20</p> <p>3 / 42 (7.14%)</p> <p>4</p> <p>28 / 42 (66.67%)</p> <p>51</p> <p>9 / 42 (21.43%)</p> <p>12</p> | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>6 / 42 (14.29%)</p> <p>7</p> | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Back pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscle spasms</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Muscular weakness</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 42 (7.14%)</p> <p>4</p> <p>5 / 42 (11.90%)</p> <p>9</p> <p>5 / 42 (11.90%)</p> <p>6</p> | | |
| <p>Metabolism and nutrition disorders</p> <p>Decreased appetite</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hypercholesterolaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>8 / 42 (19.05%)</p> <p>13</p> <p>13 / 42 (30.95%)</p> <p>21</p> | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 11 May 2016 | Implemented at sites September 2016 1. To allow patients with an unknown PgR status for sites where PgR is not routinely tested 2. Extension to the cap of known BRCA patients to 20 patients 3. Minimum required tumour size reduced from 2cm to 1.5cm to allow inclusion of patients ineligible for competing trials 4. Update to Investigator Brochure V6.0 5. Number of Streck tubes requested increased from 1 to 2 samples 6. Request for patients to consent for diagnostic tumour tissue or samples taken during surgery to be used as part of this study if samples prove to be unevaluable at analysis 7. Addition of exploratory endpoints (to include cellularity and PD-L1 expression analysis) 8. Recommendation for ultrasound guidance in performing biopsies to improve sample quality |
| 12 September 2016 | Implemented at sites January 2017 1. Modification of the screening pathway to allow the provision of diagnostic FFPE block if additional biopsy cannot be obtained for those patients where time restraints would limit patient participation 2. Number of Streck tubes requested increased from 2 to 3. 3. Recommendation for highly effective contraception whilst taking rucaparib and for 6 months afterward following updates to the reference safety information that rucaparib is embryo-toxic 4. Update to Investigator Brochure V7.0 |
| 04 November 2016 | Implemented at sites January 2017 1. Update to Investigator Brochure V8.0 2. Mandatory guidance of highly effective contraception whilst taking rucaparib for 1 month following the last dose for females and 4 months following the last dose for males as per advice from the MHRA and an update to the Investigator Brochure |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported