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

1901/2006 apply to this trial?	

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
Interruption due to patient error	1
Adverse event, non-fatal	7

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 inelibile, 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 inelibile, 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 rario				
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 ctDAN 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) Insomnia subjects affected / exposed occurrences (all)	 3 / 42 (7.14%) 5 5 / 42 (11.90%) 6		
Investigations Adjusted calcium subjects affected / exposed occurrences (all) Blood bilirubin increased subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) Haemoglobin increased subjects affected / exposed occurrences (all) Liver function test increased subjects affected / exposed occurrences (all)	 3 / 42 (7.14%) 3 7 / 42 (16.67%) 10 7 / 42 (16.67%) 8 9 / 42 (21.43%) 12 3 / 42 (7.14%) 4 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			

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

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