Clinical trial results:
A single arm, open-label, phase II study to assess the efficacy of rucaparib in metastatic breast cancer patients with a BRCAness genomic signature.

Summary

EudraCT number	2015-000580-14
Trial protocol	FR
Global end of trial date	09 January 2020

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	UC-0105/1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02505048
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
Public contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT-RAHMOUNE, UNICANCER, 33 1 71 93 67 04, n.ait-rahmoune@unicancer.fr

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	26 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the clinical benefit rate (CBR) of rucaparib in previously treated metastatic breast cancer patients with a BRCAness profile or a BRCA1/2 somatic mutation, and if significant, to assess the overall response rate (ORR).

Protection of trial subjects:

An Independent Ethics Committees reviewed and gave a favorable opinion to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.
This study was conducted in accordance with:
* The Declaration of Helsinki (1964) and subsequent amendments
* The Good Clinical Practices defined by the International Conference on Harmonization (ICH–E6, 17/07/96
* The European Directive (2001/20/CE)
* The Huriet’s law (n° 88-1138) of December 20th, 1988, relative to the protection of persons participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9th, 2004,
* The law on ‘informatics and freedom’ (Informatique et Libertés n° 78-17) of January 6th,1978 modified by the law n° 2004-801 of August 6th, 2004 relative to the protection of persons with regard to the computerized processing of personal data
* The bioethic law n°2011-814 of July 8, 2011.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	25 August 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	29
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

RUBY was a single arm, open-label, multicentric, phase II trial assessing the efficacy of the PARP inhibitor rucaparib. Patients had HER2 negative, BRCAness profile defined by Clovis genomic signature or BRCA1/2 somatic mutation, progressing breast cancer with at least one line of chemotherapy at the metastatic setting.

Pre-assignment

Screening details:

The study consisted of a 28-day screening phase to establish patients' eligibility and document baseline measurements, a treatment phase (28-day treatment cycles until disease progression), and a long-term follow-up to monitor the clinical benefit rate, progression-free survival, overall survival, and the prognostic value of the Clovis signature.

Period 1

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

Arms

Arm title	Rucaparib

Arm description:

All eligible patients entering the study received rucaparib (600 mg oral) twice daily, every day in 28-day cycles until patient withdrawal (toxicity, disease progression, or after patient’s or investigator’s decision).

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

Dosage and administration details:

All eligible patients received 600 mg oral rucaparib (2 x 300 mg tablets) twice daily, every day in 28-day cycles until toxicity, disease progression, or patient’s or investigator’s decision. Tablets should have been swallowed with at least 240 mL of water at the same time each morning, and evening without regards to meals.

Number of subjects in period 1	Rucaparib
Started	40
Completed	3
Not completed	37
Death	34
Sponsor decision	3

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	29	29	
From 65-84 years	11	11	
85 years and over	0	0	
Age continuous Units: years			
median	54		
full range (min-max)	27 to 76	-	
Gender categorical Units: Subjects			
Female	40	40	
Male	0	0	
Eastern Cooperative Oncology Group Performance status Units: Subjects			
ECOG 0	23	23	
ECOG 1	17	17	
Primary tumor phenotype Units: Subjects			
ER-/PR-	17	17	
ER-/PR+	1	1	
ER+/PR-	3	3	
ER+/PR+	19	19	
Number of previous chemotherapy received in the metastatic setting Units: Subjects			
01	17	17	
02	6	6	
03	11	11	
04	4	4	
05	1	1	
06	1	1	
Previous platinuum salts (all settings)			

Units: Subjects			
Yes	10	10	
No	30	30	

End points

End points reporting groups

Reporting group title	Rucaparib

Reporting group description:

All eligible patients entering the study received rucaparib (600 mg oral) twice daily, every day in 28-day cycles until patient withdrawal (toxicity, disease progression, or after patient's or investigator's decision).

Primary: Clinical benefice rate

End point title	Clinical benefice rate[1]

End point description:

End point type	Primary

End point timeframe:

DIsease evolution was assessed every 8 weeks until disease progression (up to 30 moths) according to RECIST evaluation.

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: The primary endpoint was the clinical benefice rate. The decision rule was that least 11 of 37 evaluable patients were required to achieve a clinical response in order to claim for the success of the study.

End point values	Rucaparib			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: percent				
number (confidence interval 95%)	13.5 (4.5 to 28.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

The Progression free survival was defined as the time from first dose of rucaparib to the disease progression assessed by RECIST or death from any cause. Patients still alive at the time of analysis without documented progression were censored at the last tumor assessment.

End point type	Secondary

End point timeframe:

30 months

End point values	Rucaparib			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: month				
median (confidence interval 95%)	1.7 (1.4 to 1.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

The Overall survival was defined as the delay between the date of inclusion to death from any cause. Patients still alive at the time of analysis (including lost to follow-up) were censored at the last known alive date.

End point type	Secondary

End point timeframe:

30 months

End point values	Rucaparib			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: month				
median (confidence interval 95%)	6.7 (5.6 to 12.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period of the study (up to 30 months after first study medication intake)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Rucaparib

Reporting group description: -

Serious adverse events	Rucaparib		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 40 (30.00%)		
number of deaths (all causes)	34		
number of deaths resulting from adverse events	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor progression			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain aggravated			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rucaparib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 40 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	16 / 40 (40.00%)		
occurrences (all)	29		
Aspartate aminotransferase increased			
subjects affected / exposed	25 / 40 (62.50%)		
occurrences (all)	44		
Blood alkaline phosphatase increased			
subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	20		
Blood bilirubin increased			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Gamma-glutamyltransferase increased			
subjects affected / exposed	23 / 40 (57.50%)		
occurrences (all)	37		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	5		
Lymphoedema			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	5		
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 40 (37.50%)		
occurrences (all)	22		
Leukopenia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Lymphopenia			
subjects affected / exposed	15 / 40 (37.50%)		
occurrences (all)	34		
Neutropenia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	12		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	28 / 40 (70.00%)		
occurrences (all)	56		

Chest pain subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 5 2 / 40 (5.00%) 7		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 4 / 40 (10.00%) 4 6 / 40 (15.00%) 7 8 / 40 (20.00%) 11 5 / 40 (12.50%) 8		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 6 / 40 (15.00%) 8		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 40 (15.00%)		
occurrences (all)	7		
Hypercholesterolaemia			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	13		
Hyperglycaemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 June 2015	Following the request of the competent authority (ANSM), the sponsor modified the information relative to contraception in the protocol and the patient consent form. A serum pregnancy test was requested before initiation of all treatment cycles. Hormonal contraception were excluded due to potential interactions with rucaparib.
17 July 2015	* The protocol was modified to specifiy the link between SAFIR02 and RUBY studies. Patients not eligible to randomization in the SAFIR02 study (but meeting all the inclusion/exclusion criteria of the RUBY study) may be included. * Rucaparib in 120 mg tablets were replaced by 200 mg tablets, the first step of the dose modification strategy was modified and the third level of dose reduction implemented to be consistent with other clinical trilas using rucaparib montherapy 600 mg b.i.d, every day in 28-day cycles.
30 June 2016	* Patients were allowed to take 2 x 300mg tablets or 3 x 200 mg tablets. * Patient who consented to participate to the ancillary study were asked for blood samples. The volume of blood collected was reduced from 30 mL to 20 mL in "Streck" tubes instead of EDTA tubes. * An independent committee of radiologist was implemented to confirm the investigator radiological-based assessment of rucaparib efficacy. * The safety section of the protocol was amended following publication of the version7 of rucaparib's investigator brochure. Particular attention of grade 3 cholesterol increase was recommended. Also, warning were introduced regarding drug-drug interaction between rucaparib and statins. This modification impacted the collection of SAE by the pharmacovigilance unit at UNICANCER. *Following the publication of the version 7 of rucaparib's investigator brochure, myelodysplastic syndrome and acute myeloid leukemia were considered adverse events of special interest.

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.

Limitations of the trial are the small number of subjects analysed, the lack of comparison (single arm study) of rucaparib with usual chemotherapy in patients with high genomic instability associated with poor outcome.

Notes: