Clinical trial results:
A phase II, randomized, multi-center study, assessing value of adding RAD 001 to Trastuzumab as preoperative therapy of HER-2 positive primary breast cancer amenable to surgery.

Summary

EudraCT number	2007-004098-24
Trial protocol	FR
Global end of trial date	31 March 2015

Results information

Result version number	v1 (current)
This version publication date	04 November 2021
First version publication date	04 November 2021

Trial information

Trial identification

Sponsor protocol code	GEP 04/0606

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00674414
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 0171936704, n.ait-rahmoune@unicancer.fr
Scientific contact	Nourredine AIT RAHMOUNE, UNICANCER, 33 0171936704, 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	20 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2015
Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the added efficacy obtained by the association of Trastuzumab with RAD001 as preoperative therapy of primary HER-2 positive breast cancer as shown by increased clinical tumor response rate.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was performed in compliance with the principles laid down in the declaration of Helsinki, good Clinical Practice and European regulation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 82
Worldwide total number of subjects	82
EEA total number of subjects	82

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)	62
From 65 to 84 years	20

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of first inclusion: 07 July 2008; Date of last inclusion: February 15th 2012; Date last patient out : March 2015

Pre-assignment

Screening details:

Main selection criteria are :
Female patients (≥ 18 years old),
with Histologically-confirmed diagnosis of invasive breast cancer, previously untreated
(patients who have been treated for cancer of the controlateral breast cancer can be
included if there is at least a 5 year time interval from last systemic treatment and randomization

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (Reference therapy)

Arm description:

Trastuzumab is administered once a week for 6 weeks.

Arm type	Active comparator
Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Dose: Loading dose 4 mg/kg then 2 mg/kg
Trastuzumab was administered once a week for 6 weeks.

Arm title	Arm B: experimental

Arm description:

Trastuzumab was administered once a week for 6 weeks
RAD001 was administered once daily for 6 weeks

Arm type	Experimental
Investigational medicinal product name	trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Dose: Loading dose 4 mg/kg then 2 mg/kg
Trastuzumab was administered once a week for 6 weeks.

Investigational medicinal product name	RAD001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

10 mg/day. Two x 5 mg tablets started at D1 and taken once daily, in the morning, during 6 weeks.

Number of subjects in period 1	Arm A (Reference therapy)	Arm B: experimental
Started	41	41
Completed	39	40
Not completed	2	1
Disease progression	1	-
Not treated	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A (Reference therapy)
Reporting group description:	
Trastuzumab is administered once a week for 6 weeks.	
Reporting group title	Arm B: experimental
Reporting group description:	
Trastuzumab was administered once a week for 6 weeks RAD001 was administered once daily for 6 weeks	

Reporting group values	Arm A (Reference therapy)	Arm B: experimental	Total
Number of subjects	41	41	82
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	31	29	60
From 65-84 years	10	12	22
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	41	41	82
Male	0	0	0

End points

End points reporting groups

Reporting group title	Arm A (Reference therapy)
Reporting group description:	
Trastuzumab is administered once a week for 6 weeks.	
Reporting group title	Arm B: experimental
Reporting group description:	
Trastuzumab was administered once a week for 6 weeks RAD001 was administered once daily for 6 weeks	

Primary: Primary efficacy endpoint

End point title	Primary efficacy endpoint
End point description:	
End point type	Primary
End point timeframe:	
After 6 week of treatment	

End point values	Arm A (Reference therapy)	Arm B: experimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	39		
Units: Number of complete or partial response	14	18		

Statistical analyses

Statistical analysis title	EFFICACY RESULTS
Comparison groups	Arm A (Reference therapy) v Arm B: experimental
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 5
Method	Chi-squared

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	Arm A
Reporting group description: -	
Reporting group title	Arm B
Reporting group description: -	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 41 (4.88%)	3 / 41 (7.32%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Immune system disorders			
Hypersensitivity reaction			
subjects affected / exposed	2 / 41 (4.88%)	0 / 41 (0.00%)	
occurrences causally related to treatment / all	2 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
MUCOSITIS ORAL			
subjects affected / exposed	0 / 41 (0.00%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abscess breast			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 41 (100.00%)	41 / 41 (100.00%)	
Investigations			
blood sugar abnormal			
subjects affected / exposed	9 / 41 (21.95%)	12 / 41 (29.27%)	
occurrences (all)	9	12	
Cardiac disorders			
Ejection fraction decreased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Arrhythmia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 41 (21.95%)	17 / 41 (41.46%)	
occurrences (all)	9	17	
Sensory disturbance			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Haemoglobin			
subjects affected / exposed	6 / 41 (14.63%)	19 / 41 (46.34%)	
occurrences (all)	6	19	
leukocytes			
subjects affected / exposed	4 / 41 (9.76%)	10 / 41 (24.39%)	
occurrences (all)	4	10	
Neutropenia			
subjects affected / exposed	2 / 41 (4.88%)	12 / 41 (29.27%)	
occurrences (all)	2	12	
Platelet count decreased			
subjects affected / exposed	0 / 41 (0.00%)	16 / 41 (39.02%)	
occurrences (all)	0	16	
General disorders and administration site conditions			
Pain			

subjects affected / exposed	11 / 41 (26.83%)	5 / 41 (12.20%)	
occurrences (all)	11	5	
Asthenia			
subjects affected / exposed	16 / 41 (39.02%)	26 / 41 (63.41%)	
occurrences (all)	16	26	
fever			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	
occurrences (all)	2	2	
Chills			
subjects affected / exposed	1 / 41 (2.44%)	2 / 41 (4.88%)	
occurrences (all)	1	2	
Infection			
subjects affected / exposed	2 / 41 (4.88%)	5 / 41 (12.20%)	
occurrences (all)	2	5	
Infusion related reaction			
subjects affected / exposed	6 / 41 (14.63%)	1 / 41 (2.44%)	
occurrences (all)	6	1	
retention water			
subjects affected / exposed	1 / 41 (2.44%)	1 / 41 (2.44%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	4 / 41 (9.76%)	5 / 41 (12.20%)	
occurrences (all)	4	5	
Diarrhoea			
subjects affected / exposed	6 / 41 (14.63%)	12 / 41 (29.27%)	
occurrences (all)	6	12	
Abdominal pain			
subjects affected / exposed	5 / 41 (12.20%)	4 / 41 (9.76%)	
occurrences (all)	5	4	
Dyspepsia			
subjects affected / exposed	2 / 41 (4.88%)	2 / 41 (4.88%)	
occurrences (all)	2	2	

Stomatitis			
subjects affected / exposed	2 / 41 (4.88%)	33 / 41 (80.49%)	
occurrences (all)	2	33	
Nausea			
subjects affected / exposed	6 / 41 (14.63%)	13 / 41 (31.71%)	
occurrences (all)	6	13	
Vomiting			
subjects affected / exposed	1 / 41 (2.44%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 41 (2.44%)	4 / 41 (9.76%)	
occurrences (all)	1	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 41 (9.76%)	23 / 41 (56.10%)	
occurrences (all)	4	23	
Dry skin			
subjects affected / exposed	2 / 41 (4.88%)	6 / 41 (14.63%)	
occurrences (all)	2	6	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 41 (7.32%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Bone pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 41 (7.32%)	4 / 41 (9.76%)	
occurrences (all)	3	4	
Metabolism and nutrition disorders			
Transaminases increased			
subjects affected / exposed	11 / 41 (26.83%)	17 / 41 (41.46%)	
occurrences (all)	11	17	
Lipids abnormal			

subjects affected / exposed	5 / 41 (12.20%)	10 / 41 (24.39%)	
occurrences (all)	5	10	
alkaline phosphatase			
subjects affected / exposed	3 / 41 (7.32%)	3 / 41 (7.32%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 February 2009	Investigators list updated
19 June 2009	Modification of some inclusion and non inclusion criteria Precision concerning the randomization procedure Precision concerning the interval between surgery and RAD001 intake Precision concerning surgery and adjuvant treatments Precision concerning HER2 status confirmation and biological material Precision concerning exams at baseline and during treatment
13 May 2011	Precision concerning inclusion and exclusion criteria Precision conserning the pharmacokinetic study of RAD001 Modification of study duration Modification of PIS/IC
09 February 2012	Name of the sponsor was modified (from FNCLCC to Unicancer)

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.

82 patients (41 in each arm) were randomized and analyzed for the primary objective. Initially 120 patients planned

concerning adverse events the "Occurrences all number" is not known, the number of patients is noted in this field.

Notes: