Clinical trial results:
"Essai multicentrique de phase II randomisé évaluant la tolérance et l'efficacité du tamoxifène seul versus association Tamoxifène-RAD001 (Everolimus), chez les patientes atteintes de cancer du sein métastatique résistant aux anti-aromatases"

Summary

EudraCT number	2006-004332-79
Trial protocol	FR
Global end of trial date	12 September 2018

Results information

Result version number	v1 (current)
This version publication date	06 July 2022
First version publication date	06 July 2022

Trial information

Trial identification

Sponsor protocol code	GINECO-BR105

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ARCAGY
Sponsor organisation address	1, place du Parvis Notre-Dame, HOPITAL HOTEL DIEU-B2 5ème étage, PARIS, France, 75181 cedex 4
Public contact	Sébastien ARMANET, ARCAGY, reglementaire@arcagy.org
Scientific contact	Thomas BACHELOT, ARCAGY, bachelot@lyon.fnclcc.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	09 September 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluer pour les 2 schémas d’administration le pourcentage de bénéfice clinique à 24 semaines

To assess whether concomitent use of RAD001 and tamoxifene allow better results of 2nd line hormonotherapy in metastatic breast cancer. This question is of great clinical importance as most of the metastatic patients with a tumor expressing hormonal receptor will already have received aromatase inhibitor as an adjuvant therapy and will correspond to the target population of this study.

Clinical benefit percentage evaluation at 24 weeks of treatment for the two arms of this study (Tamoxifen vs Tamoxifen+RAD001)

Protection of trial subjects:

Cette étude a été menée selon les recommandations :
- de la loi Bioéthique n° 2004-800 du 6 août 2004;
- de la "Déclaration d'Helsinki" révisée à Washington en 2002, Octobre 2000
- des bonnes pratiques cliniques de la conférence internationale d’harmonisation (ICH-E6 du 17/07/1996);
- de la loi Huriet (n°88-1138) du 20 décembre 1988 relative à la Protection des Personnes se prêtant à la Recherche Biomédicale et modifiée par la loi de santé publique (n°2004-806) du 9 août 2004;
- de la loi Informatique et Libertés n°78-17 modifiée par la loi n° 2004-801 du 6 août 2004 relative à la protection des personnes physiques à l'égard des traitements de données à caractère personnel;
- de la direction européenne (2001/20/CE) sur la conduite des essais cliniques

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	18 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 111
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	60
From 65 to 84 years	50
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Les inclusions dans l'étude ont eu lieu entre le 12 mars 2008 et le 19 Mai 2009. Au total, 111 patientes ont été incluses dans l'étude, 57 (51%) dans le bras A, 54 (49%) dans le bras B.

Pre-assignment

Screening details:

Avec une randomisation utilisant un ratio 1 :1 et sous l'hypothèse d'un taux de patientes perdues de vue 24 semaines après le début du traitement d'environ 5%, 110 patientes au total seront incluses dans l'étude (55 par bras).
Treize patientes ont présenté au moins une violation majeure au protocole, 8 dans le bras A et 5 dans le bras B

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	Bras A : contrôle

Arm description:

Bras contrôle

Arm type	Contrôle
Investigational medicinal product name	Tamoxifène
Investigational medicinal product code	LO2BA01
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

20mg/j

Arm title	Bras B: expérimental

Arm description:

bras expérimental

Arm type	Experimental
Investigational medicinal product name	tamoxifène
Investigational medicinal product code	LO2BA01
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

20mg/j, jusqu'à progression ou toxicité

Investigational medicinal product name	RAD001 (évérolimus)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg/j (2 x 5mg/j)

Number of subjects in period 1	Bras A : contrôle	Bras B: expérimental
Started	57	54
Completed	57	54

Baseline characteristics

Reporting groups	
Reporting group title	Bras A : contrôle
Reporting group description:	
Bras contrôle	
Reporting group title	Bras B: expérimental
Reporting group description:	
bras expérimental	

Reporting group values	Bras A : contrôle	Bras B: expérimental	Total
Number of subjects	57	54	111
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	66	62.5	
full range (min-max)	42 to 86	41 to 81	-
Gender categorical			
Units: Subjects			
Female	57	54	111
Male	0	0	0

Subject analysis sets	
Subject analysis set title	Bras contrôle
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Bras contrôle: Ce bras jouera le rôle de bras de référence, et servira à valider la mesure du taux de non progression observé dans le bras B	
Subject analysis set title	bras expérimental
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
bras expérimental	

Reporting group values	Bras contrôle	bras expérimental	
Number of subjects	57	54	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	66	62.5	
full range (min-max)	42 to 86	41 to 81	
Gender categorical Units: Subjects			
Female	57	57	
Male			

End points

End points reporting groups

Reporting group title	Bras A : contrôle
Reporting group description:	
Bras contrôle	
Reporting group title	Bras B: expérimental
Reporting group description:	
bras expérimental	
Subject analysis set title	Bras contrôle
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Bras contrôle: Ce bras jouera le rôle de bras de référence, et servira à valider la mesure du taux de non progression observé dans le bras B	
Subject analysis set title	bras expérimental
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
bras expérimental	

Primary: primary endpoint

End point title	primary endpoint
End point description:	
End point type	Primary
End point timeframe:	
Pourcentage de patientes ayant un bénéfice clinique à 24 semaines après le début du traitement .	

End point values	Bras A : contrôle	Bras B: expérimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: percent				
number (confidence interval 95%)	42.1 (29.1 to 55.9)	61.1 (46.9 to 74.1)		

Statistical analyses

Statistical analysis title	Analyse du critère principal
Statistical analysis description:	
Le test exact de Fisher (ou du Chi-2) a été utilisé pour comparer les sous groupes, le test de log rank pour comparer les courbes de survie à des fins exploratoires	
Comparison groups	Bras A : contrôle v Bras B: expérimental

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.045
Method	Chi-squared

Secondary: Time to progression

End point title	Time to progression

End point description:

End point type	Secondary

End point timeframe:

Le temps jusqu'à progression a été calculé de la date de randomisation jusqu'à la date de première mise en évidence d'une progression ou jusqu'à la date de décès par évolution néoplasique, et censuré à la date de dernières nouvelles ou à la date de décès

End point values	Bras A : contrôle	Bras B: expérimental		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	54		
Units: month				
median (confidence interval 95%)	4.5 (3.6 to 8.7)	8.6 (5.9 to 13.9)		

Statistical analyses

Statistical analysis title	temps jusqu'à progression

Statistical analysis description:

Le temps jusqu'à progression (TTP) et la survie globale seront estimés dans chaque bras de traitement par la méthode de Kaplan Meier, dans la population évaluable pour le bénéfice clinique et per protocole

Comparison groups	Bras A : contrôle v Bras B: expérimental
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	other
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.81

Adverse events

Adverse events information

Timeframe for reporting adverse events:

L'analyse de la tolérance a été effectuée mensuellement jusqu'à la visite du 6ème mois et ensuite tous les 3 mois jusqu'au 18ème mois

Adverse event reporting additional description:

L'analyse de la tolérance sera réalisée chez toutes les patientes randomisées.
Les EI ont été évalués conformément aux Critères terminologiques communs pour les événements indésirables du National Cancer Institute (CTCAE) version 3.0 .
Tous les évènements indésirables graves seront décrits par bras de traitement selon le dictionnaire MedDRA

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	Bras A : contrôle

Reporting group description:

Bras contrôle

Reporting group title	Bras B: expérimental

Reporting group description:

bras expérimental

Serious adverse events	Bras A : contrôle	Bras B: expérimental	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 57 (38.60%)	28 / 54 (51.85%)	
number of deaths (all causes)	26	13	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Meningeal carcinomatosis			
subjects affected / exposed	1 / 57 (1.75%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	4 / 57 (7.02%)	5 / 54 (9.26%)	
occurrences causally related to treatment / all	4 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	2 / 57 (3.51%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Asthenia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	2 / 57 (3.51%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mucositus			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
foot sprain			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Mood altered			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decompensation cardiac			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Leukaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 57 (0.00%)	2 / 54 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			

subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reduced general condition			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin necrosis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute renal insufficiency			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder prolapse			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Infection			
subjects affected / exposed	3 / 57 (5.26%)	5 / 54 (9.26%)	
occurrences causally related to treatment / all	0 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 57 (1.75%)	0 / 54 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type II diabetes			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of control of diabetes			
subjects affected / exposed	0 / 57 (0.00%)	1 / 54 (1.85%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Bras A : contrôle	Bras B: expérimental	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 57 (100.00%)	54 / 54 (100.00%)	
Vascular disorders			
HOT FLASHES			
subjects affected / exposed	19 / 57 (33.33%)	12 / 54 (22.22%)	
occurrences (all)	19	12	
Oedema			
subjects affected / exposed	6 / 57 (10.53%)	12 / 54 (22.22%)	
occurrences (all)	6	12	

Epistaxis			
subjects affected / exposed	2 / 57 (3.51%)	13 / 54 (24.07%)	
occurrences (all)	2	13	
Thrombosis			
subjects affected / exposed	5 / 57 (8.77%)	7 / 54 (12.96%)	
occurrences (all)	5	7	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	49 / 57 (85.96%)	44 / 54 (81.48%)	
occurrences (all)	30	39	
Fatigue			
subjects affected / exposed	30 / 57 (52.63%)	39 / 54 (72.22%)	
occurrences (all)	30	39	
Blood and lymphatic system disorders			
decreased hemoglobin			
subjects affected / exposed	20 / 57 (35.09%)	37 / 54 (68.52%)	
occurrences (all)	20	37	
decreased leukocyte count			
subjects affected / exposed	10 / 57 (17.54%)	29 / 54 (53.70%)	
occurrences (all)	10	29	
decreased lymphocyte count			
subjects affected / exposed	12 / 57 (21.05%)	26 / 54 (48.15%)	
occurrences (all)	12	26	
polymorphonuclear neutrophil			
subjects affected / exposed	11 / 57 (19.30%)	26 / 54 (48.15%)	
occurrences (all)	11	26	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	20 / 57 (35.09%)	19 / 54 (35.19%)	
occurrences (all)	20	19	
Stomatitis			
subjects affected / exposed	4 / 57 (7.02%)	30 / 54 (55.56%)	
occurrences (all)	57	54	
diarrhea			
subjects affected / exposed	6 / 57 (10.53%)	21 / 54 (38.89%)	
occurrences (all)	57	54	

Constipation			
subjects affected / exposed	13 / 57 (22.81%)	9 / 54 (16.67%)	
occurrences (all)	13	9	
Vomiting			
subjects affected / exposed	7 / 57 (12.28%)	9 / 54 (16.67%)	
occurrences (all)	7	9	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	2 / 57 (3.51%)	9 / 54 (16.67%)	
occurrences (all)	2	9	
Cough			
subjects affected / exposed	6 / 57 (10.53%)	7 / 54 (12.96%)	
occurrences (all)	6	7	
DYSPNEA			
subjects affected / exposed	11 / 57 (19.30%)	14 / 54 (25.93%)	
occurrences (all)	11	14	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 57 (7.02%)	24 / 54 (44.44%)	
occurrences (all)	4	24	
Nail disorder			
subjects affected / exposed	0 / 57 (0.00%)	8 / 54 (14.81%)	
occurrences (all)	0	8	
Prurit			
subjects affected / exposed	1 / 57 (1.75%)	7 / 54 (12.96%)	
occurrences (all)	1	7	
Infections and infestations			
Infection			
subjects affected / exposed	11 / 57 (19.30%)	19 / 54 (35.19%)	
occurrences (all)	11	19	
Metabolism and nutrition disorders			
ANOREXIA			
subjects affected / exposed	10 / 57 (17.54%)	23 / 54 (42.59%)	
occurrences (all)	10	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported