Clinical trial results:
A Randomized Multicenter Phase II Study Identifying Hormonosensivity Profiles and Evaluating the Efficacy of Anastrozole and Fulvestrant in the Neoadjuvant Treatment of Operable Breast Cancer in Postmenopausal Women.

Summary

EudraCT number	2006-006409-10
Trial protocol	FR
Global end of trial date	28 October 2016

Results information

Result version number	v1 (current)
This version publication date	06 July 2023
First version publication date	06 July 2023

Trial information

Trial identification

Sponsor protocol code	CARMINA 02/0609

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00629616
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	01 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of anastrozole and fulvestrant in term of clinical response rates (complete and partial responses) at 6 months in postmenopausal women with operable hormone receptor positive stage T2 to T4 breast carcinoma.

Protection of trial subjects:

In order to ensure the protection of the rights, safety and well-being of trial subjects, this clinical trial was conducted in accordance with the Declaration of Helsinki (1964) and subsequent amendments, ICH Good Clinical Practice Guidelines (CPMP/ICH/135/95), the European Directive (2001/20/CE) and the applicable local regulatory requirements and laws. Furthermore, independent Ethics Committees reviewed and gave favorable opinions to the study documents, including the initial protocol and all subsequent amendments, and all information and documents provided to subjects/patients.
Written informed consent was obtained from all patients prior to enrollment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 October 2007
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: 116
Worldwide total number of subjects	116
EEA total number of subjects	116

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	75
85 years and over	10

Subject disposition

Recruitment

Recruitment details:

From 02-OCT-2007 to 14-APR-2011, 116 eligible patients who had signed the study informed consent form were randomized. Thus, 59 and 57 patients were allocated to the anastrozole and fulvestrant arms, respectively. Two patients within the anastrozole arm were found, early on, in violation of the non-inclusion criteria and thereby excluded.

Pre-assignment

Screening details:

The trial consisted of a screening phase before randomization to establish eligibility, a treatment phase (4 months). Upon completion (day 120), a progress assessment was to be conducted. The treatments were to be or not extended for 2 additional months. A long-term follow-up to monitor the relapse-free, event-free and overall survivals, and safety

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	Anastrozole

Arm description:

Patients allocated to this Arm were to receive anastrozole for 4 months. Upon completion (day 120), a progress assessment was to be conducted. In case of clinical progression or clinical response rate strictly below 30%, Anastrozole treatment was to be stopped and the patient scheduled for surgery. Otherwise, anastrozole was to be administered for an additional period of two months (up to day 180).

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

Dosage and administration details:

1 mg per day of anastrozole was to be orally administered for 120 days. Upon completion (day 120), assuming the progress assessment showed an absence of clinical progression or a clinical response rate ≥ 30%, anastrozole treatment regimen was to be prolonged for 60 days (up to day 180), otherwise the treatment was to be terminated and a pre-surgery assessment conducted.

Arm title	Fulvestrant

Arm description:

Patients allocated to this Arm were to receive fulvestrant every two weeks for the first month then every 4 weeks for the next 3 months. Upon completion (day 120), a progress assessment was to be conducted. In case of clinical progression or clinical response rate strictly below 30%, fulvestrant treatment was to be stopped and the patient scheduled for surgery. Otherwise, fulvestrant was to be administered for an additional period of two months (up to day 180).

Arm type	Reference product
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg of fulvestrant was to be administered once every 15 days (D1, D15 and D29) in 2 slow (over 1 to 2 minutes) intramuscular buttocks shots (250 mg in each gluteal area) for 30 days then once every 28 days according to the same procedure for 90 more days. Upon completion (day 120), assuming the progress assessment showed an absence of clinical progression or a clinical response rate ≥ 30%, 500 mg of fulvestrant was to be administered once every 28 days for 60 more days (up to day 180), otherwise the treatment was to be terminated and a pre-surgery assessment conducted.

Number of subjects in period 1	Anastrozole	Fulvestrant
Started	59	57
Completed	55	52
Not completed	4	5
Bilateral tumor	-	1
Disease progression	2	2
Investigator decision	2	1
Patient choice	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Anastrozole
Reporting group description:	
Patients allocated to this Arm were to receive anastrozole for 4 months. Upon completion (day 120), a progress assessment was to be conducted. In case of clinical progression or clinical response rate strictly below 30%, Anastrozole treatment was to be stopped and the patient scheduled for surgery. Otherwise, anastrozole was to be administered for an additional period of two months (up to day 180).	
Reporting group title	Fulvestrant
Reporting group description:	
Patients allocated to this Arm were to receive fulvestrant every two weeks for the first month then every 4 weeks for the next 3 months. Upon completion (day 120), a progress assessment was to be conducted. In case of clinical progression or clinical response rate strictly below 30%, fulvestrant treatment was to be stopped and the patient scheduled for surgery. Otherwise, fulvestrant was to be administered for an additional period of two months (up to day 180).	

Reporting group values	Anastrozole	Fulvestrant	Total
Number of subjects	59	57	116
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)	20	12	32
From 65-84 years	35	39	74
85 years and over	4	6	10
Age continuous Units: years			
median	68	74	
full range (min-max)	53 to 92	51 to 88	-
Gender categorical Units: Subjects			
Female	59	57	116
Male	0	0	0
ECOG performance status Units: Subjects			
ECOG 0	49	50	99
ECOG 1	10	7	17
Menopausal under hormone replacement therapy Units: Subjects			
yes	21	19	40
no	38	38	76
Tumor location Units: Subjects			
Right breast	32	30	62

Left breast	27	27	54
Age <60 without hysterectomy and amenorrhea since at least 12 months, n/N (%) Units: Subjects			
yes	4	7	11
no	55	50	105
Age <60 with hysterectomy history & FSH >30 UI/L, n/N (%) Units: Subjects			
yes	0	1	1
no	59	56	115
Menopausal under hormone replacement therapy, n/N (%) Units: Subjects			
yes	21	19	40
no	38	38	76
Weigh Units: kilogram(s)			
median	65	67	
full range (min-max)	45 to 114	50 to 91	-
Menopausal age Units: year			
median	50	50	
full range (min-max)	40 to 58	39 to 60	-
Tumor size Units: millimetre(s)			
median	40	40	
inter-quartile range (Q1-Q3)	35 to 50	35 to 50	-
Tumor size Units: millimetre(s)			
median	40	40	
full range (min-max)	20 to 75	28 to 80	-
Height Units: centimetre			
median	160	159	
full range (min-max)	150 to 170	145 to 175	-

End points

End points reporting groups

Reporting group title	Anastrozole

Reporting group description:

Patients allocated to this Arm were to receive anastrozole for 4 months. Upon completion (day 120), a progress assessment was to be conducted. In case of clinical progression or clinical response rate strictly below 30%, Anastrozole treatment was to be stopped and the patient scheduled for surgery. Otherwise, anastrozole was to be administered for an additional period of two months (up to day 180).

Reporting group title	Fulvestrant

Reporting group description:

Patients allocated to this Arm were to receive fulvestrant every two weeks for the first month then every 4 weeks for the next 3 months. Upon completion (day 120), a progress assessment was to be conducted. In case of clinical progression or clinical response rate strictly below 30%, fulvestrant treatment was to be stopped and the patient scheduled for surgery. Otherwise, fulvestrant was to be administered for an additional period of two months (up to day 180).

Primary: Clinical response at 6 months

End point title	Clinical response at 6 months[1]

End point description:

The primary endpoint aimed to measure the efficacy of anastrozole vs. fulvestrant in term of clinical response rates (complete and partial responses according to RECIST v1.1 criteria) after 6 months assuming the 4 months assessment demonstrated either a stable disease or a sufficient clinical response.

Note:
CR: complete response; PR: partial response

End point type	Primary

End point timeframe:

6 months after randomisation.

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 efficacy endpoint aimed to evaluate the clinical response to treatment at 6 months in each arm, the observed response rates (complete or partial response 30%) was to be presented for each arm together with their 95% confidence interval. No direct comparison between the two arms was to be performed.

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	57		
Units: percent of patients				
number (not applicable)				
Responders (CR,PR)	52.6	36.8		
Non-Responders	47.4	63.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the breast conservation rate

End point title	Evaluation of the breast conservation rate

End point description:

The secondary efficacy objective was to evaluate the breast conservation rate in each arm, percentages of patients having benefited of conservative breast surgery will be calculated for each of the two treatment groups.

Note: As one Arm B's patient was operated outside of her assigned investigating center, no surgery details were available. Thereby this patient was not included in the breast conservation rate analysis (i.e., the Arm B population analyzed was 56 not 57).

End point type	Secondary

End point timeframe:

Percentages of patients having benefited of conservative breast surgery will be calculated for each of the two treatment groups.

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	56[2]		
Units: percent of patients				
number (not applicable)				
Conservative surgery	57.6	50.0		

Notes:

[2] - the Arm B population analyzed was 56 not 57

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the tumoral histological response

End point title	Evaluation of the tumoral histological response

End point description:

The evaluation of the tumoral histological response was based on Sataloff classification.

The histological response rate according to Sataloff classification was not different between the two arms (p=0.79).

End point type	Secondary

End point timeframe:

At time of surgery

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	56		
Units: percent of patients				
number (not applicable)				
Pathological responses	17.8	14.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Evolution of the tumor clinical size per arm

End point title	Evolution of the tumor clinical size per arm
End point description:	
Evolution of the tumor clinical size per arm after 6 months of treatment compared to baseline.	
End point type	Secondary
End point timeframe:	
After 6 months of treatment.	

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: millimetre(s)				
median (full range (min-max))				
Baseline	40 (20 to 75)	40 (28 to 80)		
6 months	20 (0 to 40)	28 (0 to 50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes un Ki67 expression over time

End point title	Changes un Ki67 expression over time
End point description:	
End point type	Secondary
End point timeframe:	
at time of surgery	

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percent				
arithmetic mean (standard deviation)				
arithmetic mean (confidence interval 95%)	-5.1 (± 9.1)	-4.6 (± 9.9)		

Statistical analyses

Statistical analysis title	Efficacy result
Comparison groups	Fulvestrant v Anastrozole
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0007
Method	paired Student t-test)

Secondary: Overall survival at 3 years

End point title	Overall survival at 3 years

End point description:

Overall survival was defined as the number of patients being alive at least 36 months after randomization.

End point type	Secondary

End point timeframe:

36 months after randomization.

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: Percent of patients				
median (confidence interval 95%)				
Overall survival at 3 years	100 (100 to 100)	98.2 (94.9 to 100)		

Statistical analyses

Statistical analysis title	Efficacy result
Comparison groups	Anastrozole v Fulvestrant

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.868

Secondary: Relapse-free survival at 3 years

End point title	Relapse-free survival at 3 years

End point description:

The relapse-free survival was defined as the time interval between the patient inclusion date and the date of relapse occurrence.

End point type	Secondary

End point timeframe:

3 years post-treatment.

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percent of patients				
median (confidence interval 95%)				
Relapse-free survival	94.9 (89.4 to 100)	91.2 (84.1 to 98.9)		

Statistical analyses

Statistical analysis title	Efficacy result
Comparison groups	Anastrozole v Fulvestrant
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.29

Secondary: Event-free survival (EFS) at 3 years

End point title	Event-free survival (EFS) at 3 years

End point description:

The event-free survival is defined as the time interval between the patient inclusion date and the date of event occurrence, up to 3 years.

End point type	Secondary

End point timeframe:

3 years post-treatment.

End point values	Anastrozole	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	57		
Units: percent of patients				
median (confidence interval 95%)				
Event-free survival (EFS)	90.9 (83.5 to 98.9)	87.6 (79.4 to 96.6)		

Statistical analyses

Statistical analysis title	Efficacy result
Comparison groups	Anastrozole v Fulvestrant
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Logrank
Dispersion value	0.35

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment.

Adverse event reporting additional description:

Toxicity was to be evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v 3.0) established by the National Cancer Institute (NCI).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	8

Reporting groups

Reporting group title	Anastrozole

Reporting group description: -

Reporting group title	Fulvestrant

Reporting group description: -

Serious adverse events	Anastrozole	Fulvestrant	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 59 (10.17%)	5 / 57 (8.77%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epidermoid carcinoma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gliosarcoma			

subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melanoma			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 59 (0.00%)	2 / 57 (3.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Surgical and medical procedures			
Basal cell carcinoma excision			
subjects affected / exposed	0 / 59 (0.00%)	1 / 57 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (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			
Cellulitis			

subjects affected / exposed	1 / 59 (1.69%)	0 / 57 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Anastrozole	Fulvestrant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
Investigations			
Increased liver enzyme levels	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Vascular disorders			
Venous thromboembolism	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Nervous system disorders			
Headache	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
General disorders and administration site conditions			
Hot flush	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Asthenia	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Injection site reaction	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Gastrointestinal disorders			
Nausea	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Vomiting	Additional description: The occurrences are not available		

subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Diarrhoea	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Reproductive system and breast disorders			
Vaginal dryness	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
vaginal bleeding	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Skin and subcutaneous tissue disorders			
Skin rash	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Musculoskeletal and connective tissue disorders			
Muscle pain	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Joint pain	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	
Joint stiffness	Additional description: The occurrences are not available		
subjects affected / exposed	58 / 59 (98.31%)	57 / 57 (100.00%)	
occurrences (all)	58	57	
Infections and infestations			
Urinary tract infection	Additional description: The occurrences are not available		
subjects affected / exposed	59 / 59 (100.00%)	57 / 57 (100.00%)	
occurrences (all)	59	57	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2008	-Protocol updates: o Modification of the Inclusion criteria #5: The number of required frozen biopsie samples before treatment inititiation updated from 1 to 2. o The type of surgery recommended after treatment was updated, TCSP was replaced by TCA (Lumpectomie with axillary node dissection) and MCSP by MCA (Mastectomy with axillary node dissection). o The efficacy criterion for partial or complete observed response rates assed by RECIST at 4 and 6 months was updated from strictly superior to 30% to superior or equal to 30%. o IRM and PET scan exams scheduled at the 4 months follow-up were restricted to the patients presenting with an insufficient clinical response (i.e., strictly below 30%). -Investigator brochure updates: FASLODEX™ (ZD9238; Fulvestrant) and ARIMIDEX™ (ZD1033; Anastrozole) brochures were updated. -Compliance update: the serious adverse event notification form was updated to comply with new FNCLCC and BECT Standard Operating Procedures. -Insurance broker contact update: the address of BiomedicInsure was updated. -Investigators' list update: Dr. Florence LEREBOURS replaced Dr Michèle TUBIANA-HULIN as coordinating investigator. -Dr. Véronique BECETTE joined the protocol drafting committee.
07 October 2009	-Protocol update: the inclusion period and global length of the trial were extended from 2 to 4 years and rom 5.5 to 7.5 years, respectively. -Study design update: optional PET scan exams wrongly scheduled every 6 months post-surgery were removed from the study design. -Administrative structure updates: o Sponsor scientific board update: Dr Jocelyne BERILLE replaced Dr. Jean GENEVE as FNCLCC's scientific director. o Study coordination: Pauline PIRES (Project Leader) teamed-up with Anne-Laure MARTIN (Project Leader) to support the study coordination.
07 October 2009	-Protocol update: modification of inclusion criteria #2: tumor size T2 updated from ≥3 cm to > 2 cm) -Investigator brochure update: FASLODEX™ (ZD9238; Fulvestrant) brochures was updated. -Investigators' list update. -Study coordination: Pauline PIRES (Project Leader) was replaced by Dr. Jérôme LEMONNIER.
13 September 2011	-Administrative structure updates: o Sponsor coordinators contact update: - j-berille@fnclcc.fr was updated to j-berille@unicancer.fr - al-martin@fnclcc.fr was updated to al-martin@unicancer.fr - j-lemonnier@fnclcc.fr was updated to j-lemonnier@unicancer.fr o Sponsor administrative update: Anne-Laure MARTIN (former Group Leader) was promoted Operational Associate Director. o Coordinating Investigator contact update: - f.lerebours@steloud-huguenin.org was updated to florence.lerebours@curie.net o Statistician contact update: - e.fourme@steloud-huquenin.org was updated to emmanuelle.fourme@curie.net -Investigator brochure updates: FASLODEX™ (ZD9238; Fulvestrant) and ARIMIDEX™ (ZD1033; Anastrozole) brochures were updated.

26 January 2012	-Administrative structure updates: o Sponsor identification update: on both the Protocol and the Informed Consent Form, the FNCLCC and BET logos and acronyms were replaced by UNICANCER and R&D UNICANCER, respectively. The logo of the UNICANCER BREAST GROUP was also added on those documents. o Sponsor contact updates: Bureau d'Etudes Cliniques et Thérapeutiques Pharmacovigilance (email pv-bect@fnclcc.fr) was replaced by R&D UNICANCER Pharmacovigilance (email pvrd@unicancer.fr). However phone and fax N° were kept unchanged. -Protocol identification update: CARMINA 02/0609 was replaced by UC-0104/0609 CARMINA02 on both the Protocol and the Informed Consent Form. -Protocol flow alteration: o Former annexes 2, 3 & 7 were removed, o ECOG performance status described in annexe 4 was incorporated in a new annexe 2, o Toxicity evaluation details were moved from annexe 8 to 5, o Molecular characteristics described in annexe 9 were moved to annexe 6, o IRM-based teatment evaluation was moved from annexe 10 to 9, o PET scan-based teatment evaluation was moved from annexe 11 to 8, o The expected/unexpected nature of the event associated with each of the investigational products were moved from annexe 6 to 4. o The Inform Consent Form and associated guidelines were no longer incorporated within annexe 2 and 3. -Sponsor Insurance: A new proof of insurance was provided.
06 December 2012	-Administrative structure updates: o Coordinating Investigator contact update: Dr. Florence LEREBOURS address was updated from “Centre René Huguenin” to “Institut CURIE - Hôpital René Huguenin”. o Statistician contact update: Dr. Emmanuelle FOURME address was updated from “Centre René Huguenin” to “Institut CURIE - Hôpital René Huguenin”. o Sponsor administrative updates: - Anne-Laure MARTIN (former Operational Associate Director) was promoted Director of Clinical and Translational Research. - Dr. Jocelyne BERILLE retired from the Scientific Director position. o Sponsor coordination contact update: information requests regarding study coordination were to be addressed to Dr. Jérôme LEMONNIER instead of Anne-Laure MARTIN. -Protocol update: all exploratory objectives involving functional IRM and PET scan imaging was now to be centralized for review and analysis at the Institut CURIE - Hôpital René Huguenin.
03 December 2013	-Investigators’ list update.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported