Clinical trial results:
Randomized, open label, multicentric phase III trial evaluating the benefit of a sequential regimen associating FEC100 and Ixabepilone in adjuvant treatment of non metastatic, poor prognosis breast cancer defined as triple-negative tumor (HER2 negative - ER negative - PR negative) or HER2 negative and PR negative tumor; in node positive or node negative patients.

Summary

EudraCT number	2006-006494-24
Trial protocol	FR BE
Global end of trial date	03 September 2020

Results information

Result version number	v1 (current)
This version publication date	05 January 2025
First version publication date	05 January 2025

Trial information

Trial identification

Sponsor protocol code	PACS 08/0610

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00630032
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UNICANCER
Sponsor organisation address	101 rue de Tolbiac, Paris, France, 75013
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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	28 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 March 2017
Global end of trial reached?	Yes
Global end of trial date	03 September 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate in non-metastatic, poor-prognosis breast cancer women the benefit from the sequential administration of 3 FEC100 followed by 3 cycles of Ixabepilone versus standard epirubicin + docetaxel based protocol on the disease-free survival at 5 years.

Protection of trial subjects:

This study was conducted in accordance with:
-the principles of ethics as stated in the last version in use of the Declaration of Helsinki,
- the Good Clinical Practices defined by the International Conference on Harmonization (ICH–E6, 17/07/96),
- the European directive 2001/20/CE on the conduct of clinical trials,
- Huriet's law (n° 88-1138) of December 20 th , 1988, relative to the protection of persons participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9 th , 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 6 th, 2004 relative to the protection of persons with regard to the computerized processing of personal data,
- bioethic law n° 2004-800 of August 6, 2004.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 166
Country: Number of subjects enrolled	France: 571
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	762
EEA total number of subjects	737

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)	667
From 65 to 84 years	95
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

PACS 08 is an open label, multicentric randomized phase III trial, comparing two treatment arms: sequential regimen (3 FEC100 + 3 docetaxel), versus sequential regimen (3 FEC100 + 3 ixabepilone) in the treatment of non metastatic, operable, poor prognosis breast cancer. 762 patients were included in 88 centres, between 17/10/2007 and 03/09/2010.

Pre-assignment

Screening details:

Prior to entering the PACS-08 trial, the triple negative or PR-/HER2- status of all patients was confirmed by a regional referent pathologist to confirm the eligibility of the patients before randomization. The treatment must begin within 49 days following the date of surgery.

Period 1

Period 1 title	Overall Period (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: 3 FEC 100 + 3 Docetaxel

Arm description:

Patients received:
• 3 cycles (1 every 21 days, cycle 1 to 3) of FEC100 consisting of epirubicin 100 mg/m² and 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
• Then 3 cycles (1 every 21 days, cycle 4 to 6) of docetaxel cycles 100 mg/m²

Arm type	Active comparator
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² every 3 weeks

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m² every 3 weeks

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² every 3 weeks

Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m² every 3 weeks

Arm title	Arm B: 3 FEC 100 + 3 Ixabepilone

Arm description:

Patients received:
• 3 cycles (1 every 21 days, cycle 1 to 3) of FEC100 consisting of epirubicin 100 mg/m² and 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
• Then 3 cycles (1 every 21 days, cycle 4 to 6) of ixabepilone cycles 40 mg/m²

Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² every 3 weeks

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg/m² every 3 weeks

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

500 mg/m² every 3 weeks

Investigational medicinal product name	Ixabepilone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

40 mg/m² every 3 weeks

Number of subjects in period 1	ARM A: 3 FEC 100 + 3 Docetaxel	Arm B: 3 FEC 100 + 3 Ixabepilone
Started	398	364
Completed	371	332
Not completed	27	32
Relapse	1	-
Consent withdrawal	4	-
Toxicity	12	26
MIssing	1	-
Other	8	-
Lost to follow-up	1	-
Protocol deviation	-	6

Baseline characteristics

Reporting groups

Reporting group title	ARM A: 3 FEC 100 + 3 Docetaxel

Reporting group description:

Patients received:
• 3 cycles (1 every 21 days, cycle 1 to 3) of FEC100 consisting of epirubicin 100 mg/m² and 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
• Then 3 cycles (1 every 21 days, cycle 4 to 6) of docetaxel cycles 100 mg/m²

Reporting group title	Arm B: 3 FEC 100 + 3 Ixabepilone

Reporting group description:

Patients received:
• 3 cycles (1 every 21 days, cycle 1 to 3) of FEC100 consisting of epirubicin 100 mg/m² and 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
• Then 3 cycles (1 every 21 days, cycle 4 to 6) of ixabepilone cycles 40 mg/m²

Reporting group values	ARM A: 3 FEC 100 + 3 Docetaxel	Arm B: 3 FEC 100 + 3 Ixabepilone	Total
Number of subjects	398	364	762
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)	50	45	95
From 65-84 years	348	319	667
85 years and over	0	0	0
Age continuous Units: years			
median	53.5	53	
full range (min-max)	24 to 70	26 to 71	-
Gender categorical Units: Subjects			
Female	398	364	762
Male	0	0	0
ECOG Units: Subjects			
ECOG 0	311	277	588
ECOG 1	35	31	66
Missing	52	56	108
Menopausal status Units: Subjects			
Premenopausal	167	155	322
Postmenopausal	231	209	440

Sex Units: Subjects			
Male	0	1	1
Female	398	363	761
ER / PR combination Units: Subjects			
ER+/PR+	6	2	8
ER-/PR-	307	280	587
ER+/PR-	85	82	167
ER-/PR+	0	0	0
HER2 status Units: Subjects			
Negative	397	363	760
Positive	1	1	2
Receptors			
TNBC: stands for triple negative breast cancer			
Units: Subjects			
TNBC [ER-/PR-/HER2-]	307	279	586
ER+/PR-/HER2-	85	82	167
Missing	6	3	9
TNBC: (ER-/PR-/HER2-)			
TNBC: stands for triple negative breast cancer			
Units: Subjects			
No	242	238	480
Yes	155	126	281
Missing	1	0	1
Estrogen Receptor Units: Subjects			
Yes	296	268	564
Missing	102	96	198
Progesteron Receptor Units: Subjects			
Yes	288	263	551
Missing	110	101	211

End points

End points reporting groups

Reporting group title	ARM A: 3 FEC 100 + 3 Docetaxel

Reporting group description:

Patients received:
• 3 cycles (1 every 21 days, cycle 1 to 3) of FEC100 consisting of epirubicin 100 mg/m² and 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
• Then 3 cycles (1 every 21 days, cycle 4 to 6) of docetaxel cycles 100 mg/m²

Reporting group title	Arm B: 3 FEC 100 + 3 Ixabepilone

Reporting group description:

Patients received:
• 3 cycles (1 every 21 days, cycle 1 to 3) of FEC100 consisting of epirubicin 100 mg/m² and 5-fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
• Then 3 cycles (1 every 21 days, cycle 4 to 6) of ixabepilone cycles 40 mg/m²

Subject analysis set title	TNBC (ER-/PR-/HER2-)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Triple-negative breast cancer (TNBC) are characterized by tumor cells which do not express any of markers: estrogen receptor (ER), the progesterone receptor (PR), and where the human epidermal growth factor 2 (ERBB2; formerly known as HER2).

Subject analysis set title	ER+/PR-/HER2-
Subject analysis set type	Sub-group analysis

Subject analysis set description:

non-TNBC (ER+/PR-/HER2-) are characterized by tumor cells which estrogen receptor (ER) positive, but do not express any of the progesterone receptor (PR) and where the human epidermal growth factor 2 (ERBB2; formerly known as HER2)

Primary: Disease-Free Survival (DFS) at 5-years

End point title	Disease-Free Survival (DFS) at 5-years

End point description:

The Disease-Free Survival (DFS) was defined as the interval between the date of randomization and the date of breast cancer relapse (local, regional or distant) or the date of invasive contralateral breast cancer or death from any cause, whichever occurs first.

End point type	Primary

End point timeframe:

5 years

End point values	ARM A: 3 FEC 100 + 3 Docetaxel	Arm B: 3 FEC 100 + 3 Ixabepilone	TNBC (ER-/PR-/HER2-)	ER+/PR-/HER2-
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	398	364	586	167
Units: percent				
number (confidence interval 95%)	79 (74.5 to 82.7)	83.4 (79.1 to 86.9)	0.77 (0.54 to 1.12)	0.86 (0.65 to 1.64)

Statistical analyses

Statistical analysis title	DSF analysis
Comparison groups	ARM A: 3 FEC 100 + 3 Docetaxel v Arm B: 3 FEC 100 + 3 Ixabepilone
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.175
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.1

Secondary: Distant Metastasis-Free Survival (DMFS) at 5-years

End point title	Distant Metastasis-Free Survival (DMFS) at 5-years
End point description:	
Distant Metastasis-Free Survival (DMFS) at 5-years is defined by the absence metastatic relapse or death from any cause.	
End point type	Secondary
End point timeframe:	
at 5 years	

End point values	ARM A: 3 FEC 100 + 3 Docetaxel	Arm B: 3 FEC 100 + 3 Ixabepilone	TNBC (ER-/PR-/HER2-)	ER+/PR-/HER2-
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	398	364	586	167
Units: percent				
number (confidence interval 95%)	82.3 (78.1 to 85.8)	87.7 (83.8 to 90.7)	0.58 (0.37 to 0.91)	1.04 (0.53 to 2.01)

Statistical analyses

Statistical analysis title	DMFS analysis
Comparison groups	ARM A: 3 FEC 100 + 3 Docetaxel v Arm B: 3 FEC 100 + 3 Ixabepilone
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.065
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.02

Secondary: Event-Free Survival (EFS) at 5-years	
End point title	Event-Free Survival (EFS) at 5-years
End point description:	
The Event-Free Survival (EFS) at 5-years is defined by the absence of an event (i.e., a local, regional or metastatic relapse, a contralateral breast cancer, a secondary cancer, or a death from any cause).	
End point type	Secondary
End point timeframe:	
5 years	

End point values	ARM A: 3 FEC 100 + 3 Docetaxel	Arm B: 3 FEC 100 + 3 Ixabepilone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	398	364		
Units: percent				
number (confidence interval 95%)	77.1 (72.3 to 81.1)	80.7 (76.0 to 84.6)		

Statistical analyses

Statistical analysis title	EFS analysis
Comparison groups	ARM A: 3 FEC 100 + 3 Docetaxel v Arm B: 3 FEC 100 + 3 Ixabepilone

Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.08

Secondary: Overall Survival (OS) at 5-years

End point title	Overall Survival (OS) at 5-years
End point description:	
The Overall Survival (OS) at 5-years is defined by the absence of death from any cause.	
End point type	Secondary
End point timeframe:	
5 years	

End point values	ARM A: 3 FEC 100 + 3 Docetaxel	Arm B: 3 FEC 100 + 3 Ixabepilone	TNBC (ER-/PR-/HER2-)	ER+/PR-/HER2-
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	398	364	586	167
Units: percent				
number (confidence interval 95%)	87.0 (83.1 to 90.0)	87.6 (83.6 to 90.6)	0.89 (0.58 to 1.36)	1.23 (0.52 to 2.9)

Statistical analyses

Statistical analysis title	OS analysis
Comparison groups	ARM A: 3 FEC 100 + 3 Docetaxel v Arm B: 3 FEC 100 + 3 Ixabepilone
Number of subjects included in analysis	762
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.897
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.42

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until 30 days after end of treatment (up to 5 years).

Adverse event reporting additional description:

For non-serious adverse events, the number of occurrences were not recorded, the number of patient affected were the only value available. Thus, the number of patient affected was entered in both "Subjects affected number" and "Occurrence all number" fields.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	ARM A

Reporting group description:

All randomized subjects having received at least one dose of chemotherapy.
The patients are analyzed according to the arm of treatment received in the cycle 4. If the cycle 4 has not been done, the arm for the analysis is Arm of randomization.
9 patients switched from Arm B to Arm A.
Safety analyses were conducted on 757 patients.

Reporting group title	Arm B

Reporting group description:

All randomized subjects having received at least one dose of chemotherapy.
The patients are analyzed according to the arm of treatment received in the cycle 4. If the cycle 4 has not been done, the arm for the analysis is Arm of randomization.
9 patients switched from Arm B to Arm A.
Safety analyses were conducted on 757 patients.

Serious adverse events	ARM A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	208 / 404 (51.49%)	158 / 353 (44.76%)	
number of deaths (all causes)	58	51	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of the cervix			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast carcinoma			

subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast ductal carcinoma			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma of tongue			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	2 / 404 (0.50%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial carcinoma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			

subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of cardia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (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	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloid leukemia, acute			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuroendocrine tumour of the lung			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ovarian cancer			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian carcinoma			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreas cancer			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary carcinoma			

subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Embolism pulmonary			
subjects affected / exposed	1 / 404 (0.25%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis cerebral vein			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	2 / 404 (0.50%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device implant			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	5 / 404 (1.24%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 404 (0.00%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	2 / 404 (0.50%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 404 (0.25%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Allergy			
subjects affected / exposed	0 / 404 (0.00%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Device complication			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device failure			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection injection site			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	0 / 404 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Auricular fibrillation			

subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ischemia			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non ST segment elevation acute coronary syndrom			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 404 (0.25%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral hypoperfusion			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy			

subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 404 (0.00%)	10 / 353 (2.83%)	
occurrences causally related to treatment / all	0 / 0	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain nerve			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory neuropathy			
subjects affected / exposed	1 / 404 (0.25%)	4 / 353 (1.13%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 404 (0.25%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplasia bone marrow			
subjects affected / exposed	1 / 404 (0.25%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile aplasia			
subjects affected / exposed	1 / 404 (0.25%)	4 / 353 (1.13%)	
occurrences causally related to treatment / all	1 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	55 / 404 (13.61%)	27 / 353 (7.65%)	
occurrences causally related to treatment / all	58 / 58	30 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			

subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	139 / 404 (34.41%)	45 / 353 (12.75%)	
occurrences causally related to treatment / all	251 / 251	129 / 130	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Ear disorder			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye infection			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's enteritis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 404 (0.00%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Epigastralgia			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction complicating hernia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis oral			
subjects affected / exposed	0 / 404 (0.00%)	6 / 353 (1.70%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 404 (0.50%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic dysfunction			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Allergic skin reaction			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dermatitis bullous			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exfoliative dermatitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fingernail discoloration			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	3 / 404 (0.74%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recall phenomenon			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematuria			

subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection urinary tract			
subjects affected / exposed	0 / 404 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Abscess soft tissue			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 404 (0.00%)	2 / 353 (0.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular pain			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain bone			
subjects affected / exposed	0 / 404 (0.00%)	1 / 353 (0.28%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Infection			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia with hypoxaemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 404 (0.00%)	3 / 353 (0.85%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	2 / 2	
Metabolism and nutrition disorders			
Hypercalcemia			
subjects affected / exposed	1 / 404 (0.25%)	0 / 353 (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	ARM A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	404 / 404 (100.00%)	353 / 353 (100.00%)	
Cardiac disorders			
Cardiovascular			
subjects affected / exposed	32 / 404 (7.92%)	33 / 353 (9.35%)	
occurrences (all)	32	33	
Nervous system disorders			
Neurotoxicity (motor)			
subjects affected / exposed	34 / 404 (8.42%)	47 / 353 (13.31%)	
occurrences (all)	34	47	

Neurotoxicity (Sensory)			
subjects affected / exposed	100 / 404 (24.75%)	152 / 353 (43.06%)	
occurrences (all)	100	152	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	327 / 404 (80.94%)	275 / 353 (77.90%)	
occurrences (all)	327	275	
Febrile neutropenia			
subjects affected / exposed	69 / 404 (17.08%)	40 / 353 (11.33%)	
occurrences (all)	69	40	
Thrombopenia			
subjects affected / exposed	74 / 404 (18.32%)	75 / 353 (21.25%)	
occurrences (all)	74	75	
Edema			
subjects affected / exposed	68 / 404 (16.83%)	47 / 353 (13.31%)	
occurrences (all)	68	47	
Neutropenia			
subjects affected / exposed	330 / 404 (81.68%)	302 / 353 (85.55%)	
occurrences (all)	330	302	
General disorders and administration site conditions			
Fever NOS			
subjects affected / exposed	85 / 404 (21.04%)	59 / 353 (16.71%)	
occurrences (all)	85	59	
Gastrointestinal disorders			
Nausea, vomiting			
subjects affected / exposed	327 / 404 (80.94%)	283 / 353 (80.17%)	
occurrences (all)	327	283	
Hepatobiliary disorders			
Hepatic disorder			
subjects affected / exposed	14 / 404 (3.47%)	31 / 353 (8.78%)	
occurrences (all)	14	31	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	313 / 404 (77.48%)	289 / 353 (81.87%)	
occurrences (all)	313	289	
Cutaneous disorder			

subjects affected / exposed	159 / 404 (39.36%)	101 / 353 (28.61%)	
occurrences (all)	159	101	
Nail condition			
subjects affected / exposed	101 / 404 (25.00%)	61 / 353 (17.28%)	
occurrences (all)	101	61	
Infections and infestations			
Infection			
subjects affected / exposed	121 / 404 (29.95%)	109 / 353 (30.88%)	
occurrences (all)	121	109	
Mucositis			
subjects affected / exposed	211 / 404 (52.23%)	173 / 353 (49.01%)	
occurrences (all)	211	173	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2007	• Patient inform consent form modification: - now includes the possibility of data trabsfer to commercial companies - sponsor insurance contact adress update • Investigators' list update • Protocol modification: - Serious addverse event form notification update to comply with the sponsor' SOP - Statistical considerations based on sample size was updated to "a relative disease-free survival risk of 0.77 and a relapse risk reduction of 23%" from a relative disease-free survival risk of 0.72 and a relapse risk reduction of 28%" - Refences modification
06 December 2007	• Investigator list update
13 May 2008	• Ixabepilone (BMS-247550) investigator brochure update • Investigators' list update
18 December 2008	• Protocol modification: inclusion criteria: - Inclusion criteria N°5 : the delay between surgery and the first treatment administration is increased from 42 to 49 days. - Inclusion criteria N°13: bilirubine level is decreased from 1.5 ULN to ≤ 1.0 ULN at inclusion - Inclusion criteria N°16: LVEF value is ≥50% instead of >50% • Protocol modification: dose adjustments and toxicities management: - Ixabepilone arm toxicities management clarification - Dose adjustment for ixabepilone passes from 25 to 20% reduction (passing from 30 mg/m2 to 32 mg/m2) - Docetaxel arm toxicities management clarification • Protocol modification: radiotherapy recommenadation precisions • Protocol modification: Ixabepilone preparation and administration update • Protocol modification: imaging : - Follow up: manadtory mamography on a yearly basis - Baseline evaluation: X-ray of the chest, liver imaging and bone scintigraphy need to be done within 3 months ahead of randomization • Investigators' list update • New investigator brochure • Administrative changes : - Contacts list update - Randomizationprocess update - Local requirement update with regard to specific protocol sections - Patient inform consent form is no longer included in the protocol
11 June 2009	• Investigators' list update
06 January 2010	• Investigators' list update
08 April 2010	• Investigators' list update

30 June 2010	• Protocol modification: - Toxicities management clarification - G-CSF use clarification - Modification of biological follow-up assessments during chemotherapy - Flowchart of investigations and study drug administration update - Hormonaux therapy recommendation updates - Treatment replacement after investigational study treatment discontinuation • Modification of trial duration: Inclusion period extended from 3 to 6 years • Change in docetaxel (taxotere®) pharmaceutical form • Modification of the patients inform consent form - Clarification regrading trial's ojectives and expected benefits - Clarification of docetaxel (taxotere®) expected toxicities - Follow-up schedule • Investigators' list update • Administrative change: contact list update
21 July 2010	• Investigators' list update
16 November 2010	• Investigators' list update
14 December 2010	• Legal and administratives changes related to the transfer of research activities from FNCLCC to Unicancer.
13 January 2012	• Investigators' list update

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 September 2010	Overall, 762 patients were included despite a planned number of 2500 due to the study premature termination on 09-SEP-2010 (all inclusions stopped the same day, The Ethic Committees and Competent Authorities were also informed). This early termination resulted from Bristol-Myers Squibb (BMS) announcement to withdraw its financial support to the PACS08 study as BMS decided to stop the worldwide development of ixabepilone. This information was received by the Steering committee on 21-JUL-2010. An extraordinary steering committee meeting was held on 09-SEP-2010 and concluded that trial was to be stopped and all inclusion terminated mostly as ixabepilone would no longer be made available to the sponsor. Due to regulatory considerations, and taking into account that ixabepilone is not marketed in Europe, the steering recommended: • To switch ixabepilone assigned patients who had not begun the sequence of treatment to the reference arm, • To switch patients who have already received one or two cycles of ixabepilone to the reference arm 3 FEC100 + 3 docetaxel as it is recommended for patients withdrawn for acute toxicities under ixabepilone treatment. • All patients included were to be followed according to the protocol	-

Notes:

Limitations and caveats

None reported