UNICANCER BREAST Group

Protocol for Adjuvant Therapy in Breast Cancer Treatment :

Protocol PACS 08

EudraCT N°2006-006494-24

UC- 0140/0610

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.

Abbreviated title: TavIx

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APPROVALS AND CONTACT DETAILS
PROTOCOL PACS 08

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.

FRENCH COMPETENT AUTHORITY	**Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)**	**Date of initial authorization: 02 May 2007**
		Ref. number: A70108-41
FRENCH ETHIC COMMITTEE	**CPP Ouest V CHU Pontchaillou Pavillon Recherche 2, rue Henri Le GUILLOUX 35033 RENNES Cedex 09**	**Date of initial approval: 07 June 2007**
		Ref. number : 07/09-626

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SYNOPSIS – PROTOCOL PACS 08

A) CLINICAL TRIAL IDENTIFICATION

SPONSOR - PROTOCOL CODE NUMBER: UC-0140/0610 PACS08

TRIAL TITLE:
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.

ABBREVIATED TITLE: TAVIX

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PLANNED NUMBER OF INVESTIGATIONNAL SITES: ca 80	NUMBER OF SUBJECTS: 2500

B) SPONSOR IDENTIFICATION

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C) TRIAL GENERAL INFORMATION

MEDICAL CONDITION: non-metastatic operable breast cancer

METHODOLOGY: open label, multicentric randomized phase III trial comparing two treatment arms: sequential regimen (3 FEC100 + 3 docetaxel), versus sequential regimen (3 FEC100 + 3 ixabepilone).

MAIN OBJECTIVE: To evaluate the benefit from sequential administration of 3 FEC100 followed by 3 cycles of Ixabepilone versus standard epirubicin+docetaxel based protocol on the disease-free survival (5 year DFS).

C) TRIAL GENERAL INFORMATION (...)

SECONDARY OBJECTIVE(S)

1 - efficacy:

- Whole population : assessment of impact of ixabepilone on:
  - the distant metastasis free survival (5 year DMFS)
  - the event free survival (5 year EFS; see definition of an event in evaluation criteria section)
  - the overall survival (5 year OS).
- Triple negative subgroup and ER+/PR-HER2- subgroup : assessment of impact of ixabepilone on the 5 year DFS, DMFS, EFS and OS.

2 - toxicity:

- To compare the safety profiles for the two chemotherapy regimens.

3 - biology:

1. gene profiling : to identify and/or validate predictive-gene expression profiles of clinical response / resistance to the two treatment regimens
2. Frozen and fixed tumor and frozen serum banking will be prospectively performed for future translational studies in both genomics and proteomics (transcriptome and proteome analyses, tissue array analyses)

4 – cost-effectiveness / quality of life sub-studies

INCLUSION CRITERIA:

1) Women aged from 18 to 70 years,
2) Histologically proven invasive unilateral breast cancer (regardless of the type),
3) Initial clinical condition compatible with complete initial resection,
4) No residual macro or microscopic tumor after surgical excision,
5) Beginning of chemotherapeutic treatment no later than day 49 after the initial surgery,
6) Node positive disease (positive sentinel node or positive axillary clearance) (N+) **or** node negative disease (N-) with the following criteria : SBR II / III and pT > 20 mm,
7) Patient presenting one of the following criteria (reviewed before randomization by referent pathologist):
   - o for N+ patients: triple negative tumor [HER2 negative and ER negative and PR negative] or [HER2 negative and PR negative status],
   - o for N- patients: triple negative tumor only [HER2 negative and ER negative and PR negative],

   Hormone receptor negativity is defined as ER<10%, PR<10% (IHC),
   HER2 negativity is defined as IHC 0-1+, or [IHC 2+ and FISH or CISH negative].
8) No clinically or radiologically detectable metastases (M0),
9) No peripheral neuropathy > 1,
10) WHO Performance status (ECOG) of 0 or 1,
11) Adequate recovery from recent surgery (at least one week must have elapsed from the time of a minor surgery (excluding breast biopsy); at least three weeks for major surgery),
12) Adequate hematological function (neutrophil count ≥ $2x10^9$/l, platelet count ≥ $100x\ 10^9$/l, Hemoglobin > 9 g/dl),
13) Adequate hepatic function: ASAT and ALAT ≤ 1.5 ULN, alkaline phosphatases ≤ 2.5 ULN, total bilirubin ≤ 1.0 ULN,
14) Adequate renal function: serum creatinine ≤ 1.5 ULN,
15) Patients accepting contraception intake during the overall length of treatment if of childbearing potential,
16) Adequate cardiac function, LEVF value ≥ 50% by Muga scan or echocardiography,
17) Signed written informed consent.

C) TRIAL GENERAL INFORMATION (...)

NON INCLUSION CRITERIA:

1) Bilateral breast cancer or patient with controlateral DCIS,
2) Any metastatic impairment, including homolateral sub-clavicular node involvement, regardless of its type,
3) Any tumor ≥ T4a (UICC1987) (cutaneous invasion, deep adherence, inflammatory breast cancer),
4) HER 2 overexpression defined as [IHC 3+] or [IHC 2+ and FISH or CISH positive],
5) Any clinically or radiologically suspect and non-explored damage to the controlateral breast,
6) Any chemotherapy, hormonal therapy or radiotherapy before surgery,
7) Concomittant treatment with the following strong inhibitors of CYP3A4 from 72 hours prior to the initiation of study therapy until end of treatment with ixabepilone or docetaxel: amiodarone, clarithromycin, amprenavir, delavirdine, voriconazole erythromycin, fluconazole, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, and saquinavir,
8) Previous cancer (excepted cutaneous baso-cellular epithelioma or uterin peripheral ephitelioma) in the preceding 5 years, including invasive controlateral breast cancer,
9) Patients already included in another therapeutic trial involving an experimental drug,
10) Patients with other concurrent severe and/or uncontrolled medical disease or infection which could compromise participation in the study,
11) LEVF < 50% (MUGA scan or echocardiography),
12) Clinically significant cardiovascular disease (e.g. unstable angina, congestive heart failure, uncontrolled hypertension (>150/90), myocardial infarction or cerebral vascular accidents) within 6 months prior to randomization,
13) Known prior severe hypersensitivity reactions to agents containing Cremophor EL,
14) Women of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and up to 8 weeks after treatment completion,
15) Women who are pregnant or breastfeeding. Adequate birth control measures should be taken during study treatment phase,
16) Women with a positive pregnancy test en enrollment or prior to study drug administration,
17) Patients with any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial,
18) Individual deprived of liberty or placed under the authority of a tutor.

EVALUATION CRITERIA:

PRIMARY (EFFICACY ENDPOINT):

- Disease Free Survival rate (DFS) at 5 years (disease is defined as a local, regional or metastatic relapse, a controlateral breast cancer, or a death of any cause).

SECONDARY:

1. Efficacy:
   - o triple negative and ER+/PR-HER2- subgroups: DFS at five years;
   - o whole population and subgroups: Distant Metastasis Free Survival (DMFS), Event Free Survival (EFS; an event is defined as a local, regional or metastatic relapse, a controlateral breast cancer, a second cancer or a death of any cause) and Overall Survival (OS) rates at five years.
2. Toxicity: CTC-AE scale version 3.0.
3. Biotheque: transcriptom and proteom analysis.
4. Quality of life: QlQ C30 / Br23.

D) DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS

DRUGS:

Drug Name (DCI)	Commercial Name	Pharmaceutical Form	Administration Route	Posology
5 fluorouracil		Infusion solution	I.V.	500 mg/m² every 3 weeks

Drug Name (DCI)	Commercial Name	Pharmaceutical Form	Administration Route	Posology
Epirubicin	Farmorubicine®	Infusion solution	I.V.	100 mg/m² every 3 weeks

Drug Name (DCI)	Commercial Name	Pharmaceutical Form	Administration Route	Posology
Cyclophosphamid	Endoxan®	Powder for injection solution	I.V.	500 mg/m² every 3 weeks

Drug Name (DCI)	Commercial Name	Pharmaceutical Form	Administration Route	Posology
Docetaxel	Taxotere®	Infusion solution	I.V.	100 mg/m² every 3 weeks

Drug Name (DCI)	Commercial Name	Pharmaceutical Form	Administration Route	Posology
Ixabepilone	NA	Powder and solvent for infusion	I.V.	40 mg/m²

THERAPEUTIC SCHEME:

After confirmation of their HER2, hormone receptor and node involvement status the patients will be randomized in the study and will receive the following treatments:

Arm A :

Cycles 1 to 3 : epirubicin 100 mg/m²
5 fluorouracil 500 mg/m²
cyclophosphamide 500 mg/m²
1 cycle = 21 days

Cycles 4 to 6 : docetaxel 100 mg/m²
1 cycle = 21 days

Arm B :

Cycles 1 to 3 : epirubicin 100 mg/m²
5 fluorouracil 500 mg/m²
cyclophosphamide 500 mg/m²
1 cycle = 21 days

Cycles 4 to 6 : ixabepilone 40 mg/m²
1 cycle = 21 days

For both arms:

- The treatment will be given every 21 days if the neutrophil count is ≥ 1,500 / mm^3 and the platelet count is ≥ 100,000 / mm^3.
- A blood cell and platelet count will be systematically performed in case of fever > 38.5°C and controlled 7 days later.

D) DESCRIPTION OF INVESTIGATIONAL MEDICINAL PRODUCTS (…)

Treatment delay and dose adaptations in case of acute toxicities:

Myelosuppression (both arms)

On day D21 : if neutrophil count < 1,500 / mm^3 or platelets < 100,000 / mm^3, the treatment is postponed for 7 days and pursued with the addition of G-CSF at each cycle for all the remaining cycles of both sequences.

On day D28 : if the neutrophil count or platelets count do not allow continuation of the treatment, the treatment will be definitively stopped.

In both arms, if no treatment delay due to neutropenia and/or if no G-CSF administration was required during the first 3 cycles, the first administration of docetaxel or ixabepilone (4^{th} cycle of the sequential regimen) will be performed without any G-CSF support. Conversely, the G-CSF will be maintained during the first cycle of docetaxel or ixabepilone in case of previous delay of treatment due to neutropenia or previous G-CSF administration.

Febril Aplasia (both arms)

In case of a fever > 38.5°c occurring during a period of medullar aplasia (neutrophil count < 500 /mm^3) and having required antibiotherapy or having lasted more than 24 hours, the treatment will be pursued with the same doses, but with addition of G-CSF in all remaining cycles of the experimental treatment (both sequences whatever the arm).

In case another febrile episode (neutrophil count < 500 /mm^3) occurs despite G-CSF, the doses of the products of the ongoing therapeutic sequence will be decreased by:

- FEC 100: 25%
- Docetaxel: 25%
- Ixabepilone: 20%

in all remaining cycles of the sequence.

Neurotoxicity

Ixabepilone

In case of a grade 2 neurotoxicity occurring during the ixabepilone sequence, the treatment will be decreased by 20% (32 mg/m²) in all remaining cycles. In case the grade 2 neurotoxicity is not resolved by decreasing the dose, ixabepilone will be definitively stopped.

Docetaxel

In case of a grade 2 neurotoxicity occurring during the docetaxel sequence, the treatment will be decreased by 25 % (75 mg/m²) in all remaining cycles.

In case the grade 2 neurotoxicity is not resolved by decreasing the dose, docetaxel will be definitively stopped.

THERAPEUTIC SCHEME (…)

Beyond chemotherapy:

(Treatments described bellow are not part of the study but local practices must be homogenized as follow):

- **Breast irradiation** is mandatory in case of conservative breast surgery for all patients and must begin within 8 weeks after the last course of chemotherapy.

  After total mastectomy, **chest wall irradiation** is mandatory for pT3-4 and/or ≥ 4N+. It is optional for intermediate risk patients (1-3N+ or pT2, grade III with lymphovascular invasion). Irradiation of internal mammary and supraclavicular nodes is mandatory for patients ≥ 4N+. It is optional in patients with 1-3N+ and in pT2N- tumors located in the inner or central quadrants of the breast. If sentinel node biopsy of internal mammary lymph nodes is done systematically, the internal mammary chain RT indication should be done according to the final results of the biopsy and investigator decision.

- Axillary irradiation is not mandatory in case of large axillary node clearance (> or = 8). In case of massive axillary nodes involvement (80 to 100%) or Positive Sentinel Node (not followed by axillary dissection), the participating center should adopt its own policies regarding the benefit/risk ratio for such irradiation.
  Participating centers should adopt the same radiation technique and the same policies for all their patients.
- **Hormonal treatment** for patients with positive estrogen receptor (ER ≥10% in immunohistochemistry)
  - Premenopausal women: tamoxifen for 5 years
  - Postmenopausal women (over the age of 60, or bilateral oophrectomy, or age ≤ 60 with a uterus and amenorrhea for at least 12 months, or age ≤ 60 without a uterus and with FSH>30 IU/l) : aromatase inhibitors (AI) for 5 years or tamoxifen if AI are contra-indicated.
  - For perimenopausal women (premenopausal status at time of randomization followed by secondary prolonged amenorrhea after chemotherapy over 1 year): tamoxifen 2/3 years + aromatase inhibitor 2/3 years or tamoxifen 5 years followed by aromatase inhibitor 2/3 years. The switch in favour of AI will be allowed only if FSH > 30 IU/l and/or oestradiol < 30 ng/l.

E) SAMPLE SIZE DETERMINATION and STATISTICAL CONSIDERATIONS

To show a benefit of 5 % in the 5-year DFS (70 % in the reference arm vs. 75 % in the ixabepilone arm) corresponding to a relative risk of 0.81 (about 20% of relapse risk reduction) 2,500 patients should be enrolled (**1,250 patients in each arm**) to ensure a power of 80 % (beta = 20 %) assuming a two-sided situation (Log rank test) and accepting a significance level of 5 %. A minimum of 682 events are to be observed for ensuring a power of more than 80 % for detecting the pre-specified 0.81 hazard ratio.

This sample will allow us to show a gain of 6 % in 5-year DFS in the triple negative subgroup (corresponding to a relative risk of 0.77 and a relapse risk reduction of 23%) with a power of 80%. This triple-negative subgroup is considered as being equal to two thirds of the whole population (i.e. about 1,700 patients).

To avoid any increase of the type I error, the second analysis will be performed only if the difference observed on the whole population (main objective) is statistically significant.

Randomizations will be stratified based on:
- center
- menopausal status (premenopausal status versus postmenopausal status at time of randomization)
- triple negative tumors versus the remainder of the population (HER2-, PR -, ER+)

After the enrolment of the first 300 patients, the hypothesis concerning the proportion of the triple negative subgroup will be verified. If the proportion of triple negative patients is not equal to two thirds of the whole population, the sample size will be re-calculated.

One interim efficacy analysis will be performed 2 years after the recruitment of the last patient. The objective of this interim analysis is to assess whether it is possible to disseminate the results of the study earlier than the final 5-year analysis. This will be possible only in case of overwhelming results in favor of one of the treatment groups. The Peto procedure will be used, considering a p-value less or equal 0.001 to declare the results as positive, in order to keep a type one error close of 0.05 for the final analysis.

F) TRIAL DURATION

INCLUSION PERIOD: 6 YEARS

TREATMENT DURATION: 5 MONTHS

FOLLOW-UP DURATION: 5 YEARS+5 YEARS OF LONG TERM FOLLOW-UP

OVERALL TRIAL DURATION: 11 YEARS (MAIN CRITERION)

TABLE OF CONTENT

1. RATIONAL OF THE TRIAL

Bonadonna [1] was the first who demonstrated that the addition of adjuvant chemotherapy (CMF) in patients presenting a breast cancer with node involvement improved disease-free survival (DFS) as well as overall survival (OS). Almost all of the clinical trials published to date confirm these results [2;3]. Recently, the mature results of taxane-based clinical trials [4,5,6,7,8,9,10,11,12] have demonstrated the benefits of adding taxanes in the adjuvant setting, in terms of DFS and OS for patients with a breast cancer with node involvement or node negative (HER2 positive or negative patients).

Despite better outcome with taxanes, some subgroups still have intermediate (basal like ER/PR/HER2 negative, HER2/PR negative) prognosis. It's important to identify biologically these subgroups and to challenge new therapeutic direction.

1.1 Synthesis of prior results

THE PACS 01 TRIAL

Clinical trial results [11]

The PACS01 trial has been reported by UNICANCER BREAST Group [11]. This multicentric, prospective study included 1999 patients randomized to receive either 6 cycles of FEC100 (5fluoro-uracil 500 mg/m²; epirubicine 100mg/m²; cyclophosphamide 500 mg/m²) or 3 cycles of FEC 100 followed by 3 cycles of docetaxel (100 mg/m²). The main end-point was DFS and secondary end-points were OS and toxicity. Tamoxifen was given after chemotherapy for postmenopausal women with ER+ and /or PR+. After a protocol amendment tamoxifen was given to all patients with ER+ and/or PR+.
The randomization was stratified on investigational center, age (less or more than 50 years old) and the number of involved nodes.
With a median follow up of 59,7 months the PACS01 trial demonstrated that the sequential use of docetaxel significantly improved DFS (78.3% vs 73.2%, HR : 0.83) and OS (90.7% vs. 86.7%; HR:0.77) compared to 6 cycles of FEC 100. This advantage was more significant for patients with 1-3 involved nodes and age ≥50 years.
Both triple negative (ER/PR/HER2 negative) and PR/HER2 negative profiles are significantly associated to a worse prognosis. Moreover, although the adjunction of docetaxel significantly improves the DFS and OS of the whole population of PACS 01, this sequential regimen does not improve significantly the outcome of the two subgroups [13, 14].

Whole population	Triple negative	Non Triple negative	
DFS, 5 years	65.5%	77.3%	p=0.001
OS, 5 years	83.3%	89.4%	p=0.004
FEC arm			
DFS, 5 years	63.0%*	74.0%	*NS*
OS, 5 years	79.8%	87.1%	*NS*
FEC-D arm			
DFS, 5 years	68.1%*	80.5%	p=0.020
OS, 5 years	87.0%	91.0%	*NS*

** Triple negative subgroup : DFS by arm not statistically significative*

Whole population	ER+/PR-/HER2-	Non ER+/PR-/HER2-	
DFS, 5 years	69.0%	76.8%	p=0.056
OS, 5 years	85.3%	89.1%	*NS*
FEC arm			
DFS, 5 years	68.1%	73,2%	*NS*
OS, 5 years	81.4%	86,8%	*NS*
FEC-D arm			
DFS, 5 years	69.9%	80.4%	p=0.047
OS, 5 years	88.8%	91.4%	*NS*

These results indicate that despite better outcome with taxanes, some subgroups (triple negative, PR negative) still have poor prognosis. These subgroups could easily be biologically defined and justify innovative treatments.

1.2 Treatment's data to be evaluated

EPOTHILONES

Taxane, paclitaxel and docetaxel, promotes the polymerization of tubulin heterodimers into MTs and stabilizes preformed MTs under various set of depolymerizing conditions [15]. In the early 1990s a second class of cytotoxic natural product was discovered. These compounds have been termed epothilones. Epothilone possesses a paclitaxel-like mechanism of action [16]. Epothilones are secondary metabolites that are produced by myxobacteria, *Sorangium cellulosum*. Two major fermentation products were reported, epothilone A and epothilone B, that differ only by the absence or presence of a methyl group at the trisubstituted epoxide moiety [17]. However, in contrast to paclitaxel, epothilones were also shown to inhibit the growth of cells overexpression, the P-gp efflux pump [18]. Epothilone have also been quoted as being significantly more water soluble than paclitaxel.

Epothilones have been the subject of an extensive chemistry effort, which has culminated in no less than 17 different total syntheses of these natural products. Their most promising agent are deoxy-epothilone B, deoxy-epothilone F and the 15-deoxy-15-aza-epothilone (Ixabepilone) [19,20] .

Ixabepilone

- ***Preclinical data***

Ixabepilone is developed by Bristol Meyer Squibb [21]. It is a lactam analogue of epothilone B and has a mode of action similar to that of paclitaxel inducing MTs stabilization. Ixabepilone induces cell cycle arrest in G2/M transition and subsequent apoptotic cell death. Yamagushi *et al*. demonstrated in MDA-MB 468 cell, that ixabepilone induces apoptosis through a Bcl-2 suppressible pathway that controls a conformational change of the pro-apoptotic BAX protein [22].
Ixabepilone was as active as epothilone B in inducing cytotoxicity in a large panel of cancer cell lines and human tumor models.
Ixabepilone retains its antineoplastic activity in cancer cells and human tumor models that have developed resistance to paclitaxel, overexpression of P-gp or mutation of β-tubulin.

- ***Clinical data***

Ixabepilone demonstrated definite activity in metastatic setting for patients resistant to anthracycline (ORR= 42%) or resistant to anthracyclines and taxanes (ORR= 12-22%) or resistant to anthrayclines-taxanes and capecitabine (ORR=18%).

Phase I trials [23,24,25]

In one phase I monotherapy study, ixabepilone was administered once a day every 3 weeks. 31 patients were treated at 6 dose levels. One patient at the first level (30mg/m²) presented a hypersensitivity reaction. Hypersensitivity reaction was prevented by oral antihistaminics (H1/H2). At the level of 65 mg/m², two patients experienced grade 4 neutropenia. At the level 50 mg/m² no DLT was observed and an antitumor activity was seen: 1 complete response, 3 partial responses and 11 stable diseases. The PK/PD of Ixabepilone appears to be linear and produce dose-dependant increase of tubulin polymerization in peripheral blood mononuclear cells. Three others phase I were reported in combination with carboplatinum or irinotecan or capecitabine.

Ixabepilone and breast cancer in metastatic setting

Clinical trial in patients previously treated by anthracyclines [26]

Patients enrolled in this study had metastatic breast cancer and were previously treated with an anthracycline in the adjuvant and/or neoadjuvant setting. To avoid neuropathies seen with the original 50 mg/m^2 over 1 hour regimen the infusion duration was extended to 3 hours. After observing increased mucositis and abdominal pain in patients treated with this regimen in other studies, the dose was reduced to 40 mg/m^2 over 3 hours every 21 days. Sixty-five women have been enrolled to the 40 mg/m^2 3-hour regimen; preliminary safety data are now available on 38 patients over 145 cycles. Average age of the patients was 51 years (range 33-70 years) and the baseline ECOG performance status was equal to 0, 1, or unknown in respectively 19, 17, and

2 patients. Grade 3/4 neutropenia incidence was 24%/24%. Grade 3/4 non hematological toxicities occurred in 44% of patients and included myalgia (11%), arthralgia (5%), and fatigue (5%). Grade 3 neuropathy was equal to 16% compared to 37% for the 50 mg/m^2 per 1 hour regimen. Overall response rate was 41%(29-54), median duration of response 8.2 months and overall survival 22 months. This analysis indicates that Ixabepilone, administered at the dose of 40 mg/m^2 IV over 3 hours, is an active therapy and has acceptable safety in patients with metastatic breast cancer who have received prior (neo)adjuvant anthracycline therapy.

Clinical trial in patients previously treated by anthracyclines and taxanes [27]

This study was designed to evaluate the efficacy and safety of Ixabepilone in women with metastatic breast cancer previously treated with both an anthracycline and a taxane. Patients must have progressed during or within 4 months of their taxane therapy for metastatic disease (6 months of adjuvant therapy). To avoid neuropathies seen with the initial 50 mg/m^2 over 1 hour regimen, the infusion duration was extended to 3 hours. After observing increased mucositis and abdominal pain in patients treated with this regimen in other studies, the dose was reduced to 40 mg/m^2 over 3 hours every 21 days.
Forty-nine women have been enrolled to the 40 mg/m^2/3-hour regimen; preliminary safety data are now available on 42 patients over 148 cycles. Median age was 52 years (range 30-81 years); ECOG PS 0/1 in 10/32; and 38 of 49 patients progressed within 30 days of last taxane dose. Grade 3 and 4 neutropenia occurred in 40% and 20%, respectively. Febrile neutropenia incidence was 5%. Drug-related Grade 3/4 non hematologic toxicities occurred in 36% of the patients and included: fatigue (21%), myalgia (7%), nausea/vomiting (5% each), constipation (5%), and diarrhea (2%). Grade 3 sensory neuropathy was 7% compared to 25% for the 50 mg/m^2/1-hour regimen. Among the 28 patients, now out of the study, only 1 (3.6%) discontinued due to peripheral neuropathy (at Cycle 7) compared to 25% for the 50 mg/m^2/1-hour regimen. Preliminary efficacy data collected on 49 patients have been reported: partial responses were reported in 6 patients and stable disease (SD) in 22 patients (4 SD patients are still ongoing). Four of the six responders had previously progressed within 1 month of their last taxane dose and at least 2 have received Ixabepilone for a longer duration than their prior taxane. Eight SD patients have received 6 cycles or more. This preliminary analysis indicates that Ixabepilone, administered at 40 mg/m^2 IV over 3 hours, has a favorable safety profile and is active in patients with anthracycline pre-treated and strictly defined taxane-resistant metastatic breast cancer.

Clinical trial in patients previously treated by anthracyclines, taxanes and capecitabine [28]

This study was designed to evaluate the efficacy and safety of Ixabepilone in women with metastatic breast cancer previously treated with both an anthracycline, a taxane and capecitabine. One hundred twenty six have been enrolled to the 40 mg/m^2/3-hour regimen.
Grade 3/4 neutropenia incidence was 31%/23%. Grade 3/4 non hematological toxicities included grade 3/4 sensory neuropathy (14%/1%). Overall response rate was 18%, median duration of response 5,7 months and overall survival 8,6 months.

Ixabepilone in neoadjuvant setting [29]

Women with invasive stage IIA-IIIB breast cancer with tumors ≥3 cm diameter received 40 mg/m2 ixabepilone as a 3-hour infusion on Day 1 for up to four 21-day cycles, followed by surgery within 3-4 weeks of completion of chemotherapy. Biopsies for analysis of mRNA expression were obtained both pre- and post-therapy. Adjuvant chemotherapy with an anthracycline combination regimen followed by radiotherapy and tamoxifen were administered as indicated. Pathological response was assessed using the Sataloff criteria. A total of 164 patients were enrolled. Preliminary results are available for 96 patients.
Median age was 56 years (range 27-79) and 99% were ECOG 0. TNM status T2/T3/T4 was 57%/23%/16%, Grade 1/2/3/unknown was 11%/40%/24%/25% and ER status of +/-/unknown was 51%/46%/3%. A complete pathological response (pCR) in the breast was achieved in 19 patients (19%), of whom 13 (13%) also had pCR in the axillary lymph nodes. Grade 3/4 neutropenia occurred in 14%/5%. Grade 2 toxicities for arthralgia/myalgia neuropathy and mucositis were 23%, 12% and 3%; grade 3 toxicities were 2%, 2% and 1% respectively. ER has been identified as predictive marker for the treatment response of ixabepilone.

Conclusion:

Ixabepilone demonstrated definite activity in metastatic setting for patients resistant to anthracycline (ORR= 42%) or resistant to anthracyclines and taxanes (ORR= 12-22%) or resistant to anthrayclines-taxanes and capecitabine (ORR=18%).
Roché et al. demonstrated that Ixabepilone is active in triple negative (HER/ER/PR negative) patients in neoadjuvant and metastatic setting [30].

Efficacy in neoadjuvant trial:

	Triple negative: n=42	Non triple negative: n=119
ORR , n, (%)	27 (64)	71 (60)
pCR breast, n (%)	11 (26)	18 (15)
pCR breast+ lymph nodes, n(%)	8 (16)	9 (8)

Efficacy in metastatic setting (patients anthracyclines pretreated):

	Triple negative : n=11	Non triple negative: n=54
ORR, n, (%)	6 (55)	21 (39)
Duration of response month	4,6	8,3
PFS, month	4,6	5,7

Ixabepilone has notable clinical activity in breast cancer patients with triple-negative tumors, a population with extremely limited treatment options and poor prognosis in arm FEC-D of the PACS 01 trial. Ixabepilone represents a promising therapeutic option for these patients in the adjuvant setting.

Node negative patients with poor prognosis and who did not receive adjuvant treatment show the same evolutivity profile as node positive patients. Adjuvant chemotherapy improves both recurrence free and overall survival in these patients. The intergroup trial [8] shows that with a taxane-based (docetaxel) anthracycline free regimen the recurrence risk was decreased by 27%. Thus, it seems legitimate to offer a chemotherapy comprising taxane to these patients.

The objective of this prospective, multicentric, phase III clinical trial is to evaluate 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 with node positive disease (HER2 negative-ER negative-PR negative) or HER2 negative and PR low (less than 10% in immunochemistry) in patients with node positive or node negative disease.

2. TRIAL'S OBJECTIVES

2.1 Main Objective

The main objective of this trial is to evaluate 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. *See definition of the DFS section 10.1.*

2.2 Secondary Objectives

2.2.1 – Efficacy

- For the Whole Population : to compare the impact of ixabepilone and docetaxel on the distant metastasis free survival (DMFS), the event free survival (EFS) and the overall survival (OS). *See definition of an event section 10.2.1.*

- For both Triple Negative subgroup and [ER+/ PR-/HER2-] subgroup : to compare the impact of ixabepilone and docetaxel on the DFS, DMFS, EFS and OS.

2.2.2 – Toxicity

- To compare the safety profiles of the two sequential chemotherapy regimens.

2.2.3 - Biology

- Gene profiling: to identify and/or validate predictive gene expression profiles of clinical response / resistance to the two sequential treatment regimens.

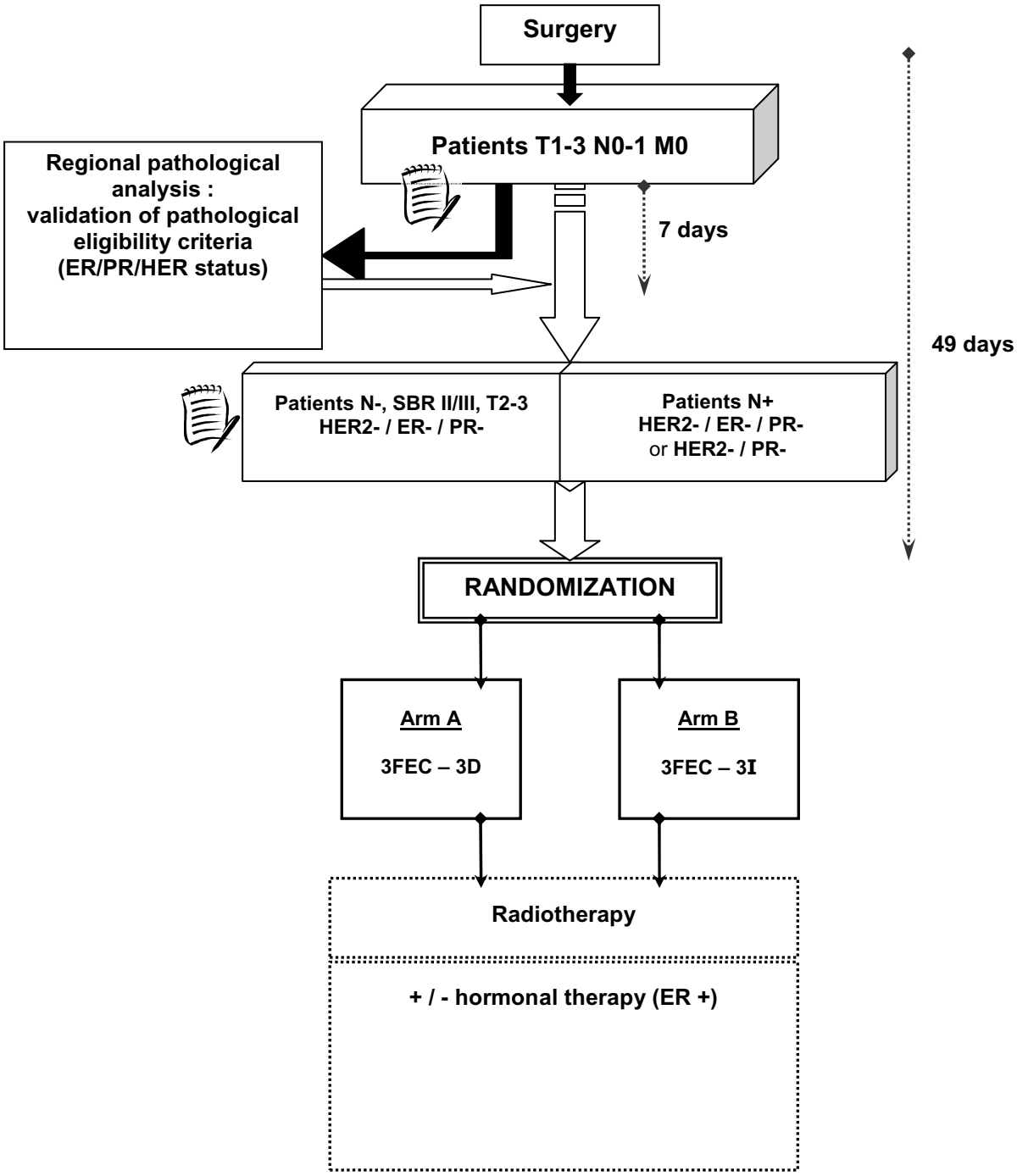
- Frozen and fixed tumor and frozen serum banking will be prospectively performed for future translational studies in both genomics and proteomics (transcriptome and proteome analysis, tissue array analysis).

2.2.4 – Other objectives

- Cost-effectiveness evaluations.
- Assessment of the quality of life in both groups of patients.

3. METHODOLOGY

This trial 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.



4. PATIENT SELECTION

4.1 Inclusion Criteria

All the following conditions are to be fulfilled:

1) Women aged from 18 to 70 years,
2) Histologically proven invasive unilateral breast cancer (regardless of the type),
3) Initial clinical condition compatible with complete initial resection,
4) No residual macro or microscopic tumor after surgical excision,
5) Beginning of chemotherapeutic treatment no later than day 49 after the initial surgery,
6) Node positive disease (positive sentinel node or positive axillary clearance) (N+) **or** node negative disease (N-) with the following criteria : SBR II / III and pT>20mm,
7) Patient presenting one of the following criteria:
   - for N+ patients: triple negative tumor [HER2 negative and ER negative and PR negative] or [HER2 negative and PR negative status],
   - for N- patients: triple negative tumor only [HER2 negative and ER negative and PR negative]

   HER 2 negativity is defined as IHC 0, or IHC 1+, or [IHC 2+ and FISH or CISH negative].
   Hormonal receptor (progesterone and estrogen receptors) negativity is defined as a rate <10% in immunohistochemistry.
   All tumors will be centrally analysed before randomization by a regional web of reference pathologists to assess final diagnosis of HER2 expression and hormonal receptor status.
8) No clinically or radiologically detectable metastases (M0),
9) No peripheral neuropathy > 1,
10) WHO Performance status (ECOG) of 0 or 1,
11) Adequate recovery from recent surgery (at least one week must have elapsed from the time of a minor surgery (excluding breast biopsy); at least three weeks for major surgery),
12) Adequate hematological function (neutrophil count $\geq 2x10^9$/l, platelet count $\geq 100x\ 10^9$/l, Hemoglobin > 9g/dl),
13) Adequate hepatic function: ASAT and ALAT $\leq$ 1.5 ULN, alkaline phosphatase $\leq$ 2.5 ULN, total bilirubin $\leq$ 1.0 ULN,
14) Adequate renal function: serum creatinine $\leq$ 1.5 ULN,
15) Patients accepting contraception intake during the overall length of treatment if of childbearing potential,
16) Adequate cardiac function, LEVF value $\geq$ 50% by Muga scan or echocardiography,
17) Signed written informed consent.

Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the last dose of chemotherapy in such a manner that the risk of pregnancy is minimized. WOCBP include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophrectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 30 IU/l]. Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to the start of study medication.

4.2 Non-inclusion Criteria

1) Bilateral breast cancer or patient with controlateral DCIS,
2) Any metastatic impairment, including homolateral sub-clavicular node involvement, regardless of its type,
3) Any tumor ≥ T4a (UICC1987) (cutaneous invasion, deep adherence, inflammatory breast cancer),
4) HER2 overexpression defined as [IHC 3+] or [IHC 2+ and FISH or CISH positive],
5) Any clinically or radiologically suspect and non-explored damage to the controlateral breast,
6) Any chemotherapy, hormonal therapy or radiotherapy before surgery,
7) Concomittant treatment with the following strong inhibitors of CYP3A4 from 72 hours prior to the initiation of study therapy until end of treatment with ixabepilone or docetaxel: amiodarone, clarithromycin, amprenavir, delavirdine, voriconazole erythromycin, fluconazole, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, and saquinavir.
8) Previous cancer (excepted cutaneous baso-cellular epithelioma or uterin peripheral ephitelioma) in the preceding 5 years, including invasive controlateral breast cancer,
9) Patients already included in another therapeutic trial involving an experimental drug,
10) Patients with other concurrent severe and/or uncontrolled medical disease or infection which could compromise participation in the study,
11) LEVF < 50% (MUGA scan or echocardiography),
12) Clinically significant cardiovascular disease (e.g. unstable angina, congestive heart failure, uncontrolled hypertension (>150/90), myocardial infarction or cerebral vascular accidents) within 6 months prior to randomization,
13) Known prior severe hypersensitivity reactions to agents containing Cremophor EL,

14) Women of childbearing potential who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and up to 8 weeks after treatment completion,

15) Women who are pregnant or breastfeeding. Adequate birth control measures should be taken during study treatment phase,

16) Women with a positive pregnancy test en enrollment or prior to study drug administration,

17) Patients with any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial,

18) Individual deprived of liberty or placed under the authority of a tutor.

5. RANDOMIZATION

Screening : prior to entering into the PACS 08 trial, all patients defined by a local non reference pathologist as triple negative or PR-/HER2- patient should be requested to sign a screening informed consent to consent to the sending of a tumor sample to the local reference pathologist for validation of the pathological diagnosis, and will be registered in a screening file.

After the basal assessment and all inclusion / non inclusion criteria are validated and the “study” written informed consent is signed, the eligible patients will be randomized to receive either the arm A regimen (3 FEC100 + 3 docetaxel) or the arm B regimen (3 FEC100 + 3 ixabepilone).

Patient’s randomization is performed via a web platform (ATLANSTAT). To randomize patients, please connect to the website: www.atlanstat.com.
For further information, please refer to the current randomization’s SOP.

Randomization will be stratified based on:

- the center,
- the menopausal status (premenopausal versus postmenopausal patients),
- triple negative patients (HER2- / PR- / ER-) versus the remainder of the population (HER2- / PR– patients)

The treatment must begin within 49 days following the date of surgery.

6. TREATMENTS

6.1 Description of the treatment to be evaluated

Ixabepilone
Ixabepilone for injection and its vehicle for constitution (diluent) will be supplied by BMS Pharmaceutical Research Institute.

Ixabepilone (BMS-247550) is a semi synthetic derivative of the natural product epothilone B, a non-taxane tubulin polymerization agent obtained by fermentation of the myxobacteria *Sorangium cellulosum*. Ixabepilone has a molecular formula of $C_{27}H_{42}N_2O_5S$ and its molecular weight is 506.71 grams/mole. Ixabepilone for injection is supplied as a lyophilized, white to off-white, whole or fragmented cake in a vial. The drug product is available as a 15 mg/vial. The vial containing vehicle for constitution of ixabepilone for injection, 8.0 mL/vial, will be supplied with the freeze dried product. The vehicle is a mixture of dehydrated alcohol + BMS-purified polyoxyethylated castor oil, which appears as a clear to slightly hazy, colorless to pale yellow solution. One vial of 8.0 mL/vial vehicle product is provided whenever a 15 mg/vial of ixabepilone for injection is supplied.

Packaging:
Both ixabepilone for injection and vehicle for constitution are packaged in Type I glass vials, stoppered with butyl rubber closures and sealed with aluminum seals. A sufficient excess of drug and vehicle is provided in the respective vials to allow for withdrawal losses.

Storage requirements / Stability:
Ixabepilone for injection should be stored refrigerated at 2°C to 8°C (36 to 46°F) and should be protected from light. The vehicle for constitution should be stored at 2°C to 8°C or 2°C to 25°C. If the vehicle is refrigerated, it must be allowed to warm to room temperature before constitution of the lyophile. After initial constitution with the accompanying vehicle, the solution may be stored in the vial for a maximum of one hour at room temperature and room light. The constituted solution should not be stored in the syringe. After final dilution with LRI to ixabepilone concentration between 0.2 mg/mL and 0.6 mg/mL, the solution is stable when stored at room temperature and room light for a maximum of 6 hours. Administration of the entire infusion volume must be completed within the 6-hour time period as noted above. LRI should be used to flush the IV line or extension set at the end of the infusion.

Preparation and Administration:
Prior to constitution of the lyophile, the vehicle should be kept at room temperature for approximately 1 hour. Using a suitable syringe, slowly inject the appropriate volume of vehicle into the vial of ixabepilone. Gently swirl the vial until the lyophile is completely dissolved. When completely dissolved the solution concentration of ixabepilone is 2 mg/ml. This solution must be further diluted to a final ixabepilone concentration ranging from 0.1 mg/mL to 0.6 mg/mL before administration to the subject.
For dilution, an infusion fluid that maintains the stability of ixabepilone must be used, such as:

- Lactated Ringer's Injection (LRI) with pH from 6.0 to 7.5
- PLASMA-LYTE A Injection pH 7.4® with pH from 6.5 to 8.0

- 0.9% Sodium Chloride Injection, with pH adjusted to > 6.0 with Sodium Bicarbonate Injection.

Withdraw the appropriate volume of the constituted solution containing 2 mg/mL of active drug, and transfer the constituted solution into the IV bag containing the appropriate volume of infusion fluid to achieve the final desired concentration of ixabepilone.
Dilution in a 250 mL infusion bag is sufficient in most cases to obtain the final required concentration of ixabepilone.
The infusion must be administered through an appropriate inline filter with a microporous membrane of 0.22 to 5.0 microns. Infusion fluid should be used to flush the IV line or extension set at the end of the infusion if flushing is required. Any remaining solution should be discarded according to the institutional procedures for cytotoxics.

Note 15 mg/vial: The label fill for the drug is 15 mg/vial lyophile, which is to be constituted to a concentration of 2 mg/ml with the vehicle. To account for via/needle/syringe (VNS) loss the actual amount of drug in the vial is 16 mg (+/- 3%). Hence the drug should be constituted using 8.0 mL of the vehicle for constitution (to achieve a concentration of ixabepilone of 2 mg/ml).

The following infusion components have been qualified for use with Ixabepilone:

IV sets containing an in-line 0.22 micron filter:

- Baxter Vented Paclitaxel Set (Catalog # 2C7553)
- Abbott Primary IV Plumset (Catalog #11947)

IV sets **not** containing an in-line 0.22 micron filter:

- McGaw AccuPro Pump Nitroglycerin IV Set (Catalog # V8333)
- Clintec IV Fat Emulsion Set (Catalog # 2C1105)

Filter Extension Sets (to be used with IV sets not containing an in-line filter):

- Braun Filtered Extension Set with 5 Micron Filter (Catalog #FE-5010Y)

The infusion must be administered through an appropriate in-line filter with a microporous membrane of 0.20 to 5.0 microns.
Diluted ixabepilone solutions may also be administered using a syringe pump and polyethylene-lined extension sets.

Incompatibilities:
In order to minimize subject exposure to the plasticizer di-(2-ethylhexyl)phthalate (DEHP) which may be leached from some brands of polyvinyl chloride (PVC) infusion bags or administration sets, diluted ixabepilone solutions should be stored in bottles (glass, polypropylene) or plastic bags (polyethylene, polypropylene, polyolefin, ethylene-vinyl-acetate) and administered through polyethylene-lined administration sets plasticized with TOTM (trioctyl trimellitate). IV sets and components, including filters 0.20 to 0.22, typically used for the administration of paclitaxel, have been found to be compatible with infusions of BMS-247550. Lactated Ringers Injection (LRI) in non-DEHP Excel® bags is available from B. Braun McGaw, Inc., and can be used for preparing the infusion.

Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

6.2 Labeling of treatment products

Investigational drugs supplied by the sponsor (Ixabepilone and docetaxel for N-patients randomized in arm A) will be labeled in accordance with the guidelines of the annex 13 of the EEC directive: Good Manufacturing Practices for the manufacture of investigational medicinal products (revised and adopted in July 2003).
Other medicinal products will be supplied by the pharmacies of the health care centers. Packaging will be made by the CRO CREAPHARM.

6.3 Dispatch, distribution and accounting

The distribution of the investigational medicinal products supplied to the health care centers' pharmacies by the sponsor will be performed by CREAPHARM in conformity with the Good Distribution Practices.

The pharmacist of the health care centre will acknowledge reception of all shipments by returning to the distributor a duly completed receipt.

Investigational medicinal products will have to be stored in locked room with limited access and in accordance with the recommendations of the manufacturer (see section 6.1).

It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. The pharmacist of the health care centre will keep accurate records of the drugs delivered, used, unused and/or returned by the patient.

The clinical research assistant mandated by the sponsor will be in charge of verifying the accounting records for the supplied medicinal products and ensure that an accounting form is validated and signed by the pharmacist of the health care center prior to any demand for destruction.

Drug destruction:

Unused investigational product will be destroyed on site. It is Investigators responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented..

6.4 Course of the Treatment

6.4.1 Adjuvant chemotherapy

After randomization, the patients will receive one of the following treatments within 49 days after surgery:

Arm 1:

Cycles 1 to 3: D1: epirubicin 100 mg/m²
D1: 5 fluorouracil 500 mg/m²
D1:cyclophosphamide 500 mg/m²
1 cycle = 21 days

Cycles 4 to 6: D1: docetaxel 100 mg/m² , 1-hour IV infusion
1 cycle = 21 days

Premedication:
A pre-medication will be systematically associated to the treatment on the first cycle and all the others as well:
- prednisolone (Solupred®) 50 mg, oral route, at H -12, H -3 et H - 1, that is to say the day before, the morning and an hour before the docetaxel injection, then 60 mg every 12 hours the next 2 days (H+12,H+24,H+36), i.e. 6 intakes in total.
- or methylprednisolone (Medrol®), 48mg at each intake according the same modalities as described above.

Arm 2:

Cycles 1 to 3: epirubicin 100 mg/m²
5 fluorouracil 500 mg/m²
cyclophosphamide 500 mg/m²
1 cycle = 21 days

Cycles 4 to 6: ixabepilone 40 mg/m² , 3-hour IV infusion.
1 cycle = 21 days

Premedication:
All patients must be premedicated before each treatment with Ixabepilone to prevent a hypersensitivity reaction. The regimen described below (regimen 1) is the premedication regimen recommended for routine use:
Regimen 1 : premedicate approximately one hour prior to the infusion of Ixabepilone with:

a) Oral H_1 blocker (may consist of diphenhydramine 50 mg or equivalent H_1 blocker), and
b) Oral H_2 blocker (may consist of ranitidine 150 - 300 mg or cimetidine 300 - 800 mg or nizatidine 150 - 300 mg or famotidine 20 - 40 mg or other H_2 blocker).

Note that, in the event of patient intolerability to the antihistamines specified, alternatives may be substituted at the Investigator's discretion. In addition, if the specified antihistamine is not available, alternate antihistamines may be substituted (including intravenous formulations at equivalent doses).

Patients will receive a 3-hour IV infusion of ixabepilone at 40 mg/m^2. Study therapy will be administered on Day 1 of every 21-day cycle, for a maximum of 3 continuous cycles. A cycle may be delayed for a maximum of 2 weeks due to drug-related toxicity. See Section 6.5 for re-treatment criteria.
Patients who experience unacceptable toxicity at any cycle will be discontinued from ixabepilone. Subsequent therapy for these patients is at the investigator's discretion.

The details of preparation of ixabepilone infusion are described in section 6.1.

A nurse must be present in the immediate treatment area throughout the infusion. A physician must be in close proximity to the patient treatment area.

Hypersensitivity Reactions
Ixabepilone is formulated in polyoxyethylated castor oil (Cremophor®EL), thus, hypersensitivity reactions may occur. Therefore, patients should be monitored closely for any signs or symptoms of hypersensitivity. Appropriate emergency equipment and medications (e.g., epinephrine, corticosteroids, antihistamines) should be made available in the event of an HSR. Refer to Section 6.7.3 for additional recommended premedication regimens (Regimen 2 and 3) to prevent hypersensitivity reactions in patients who developed hypersensitivity reactions despite premedication with Regimen 1.
A hypersensitivity reaction will generally occur within seconds or minutes of drug administration. Reactions may include urticaria, dyspnea, bronchospasm, angiodema, hypotension, tachycardia or occasionally cardio-respiratory arrest. In case of hypersensitivity reactions, the Investigator should institute treatment measures deemed medically appropriate.

For both arms:

- The treatment will be performed every 21 days if the neutrophil count is ≥ 1,500 / mm^3 and the platelet count is ≥ 100,000 / mm^3.
- A blood cell and platelet count will be systematically performed in case of fever > 38.5°C and controlled 7 days later.
- If the calculated body surface area is greater than 2.2 m², the administered dose will be established on the basis of 2.2 m² and will not exceed that value.
- In calculating surface areas, actual heights and weights should be used. Adjustments will not be made to "ideal" weight.
- The total dose delivered should be rounded to the nearest mg.
- After confirming that the required volume of experimental drug has been administered, the solution remaining in the line and container should be disposed of per institution policies for cytotoxics disposal.
- The use of refrigerated helmets is allowed.

6.5 Dose adaptation

The following adaptation concerning dosage and schedule of administration must be done in case of acute toxicities.
No dose re-escalation will be allowed after dose reduction.
Only one dose reduction will be allowed.
If toxicities listed below recur after dose reduction, treatment should be discontinued and the patient should switch to FEC or TAXOTERE regimen.

6.5.1 Hematological toxicities

Myelosuppression (both arms)
On day D21 : if neutrophil < 1,500 / mm^3 or platelets < 100,000 / mm^3, the treatment is postponed for 7 days and pursued with the addition of G-CSF (Neulasta®) at each cycle for all the remaining cycles of both sequences.
On day D28 : if the neutrophil or platelets count does not allow re-treatment (neutrophil <1,500/mm^3 or PLT<100,000/ mm^3), the treatment will be definitively stopped.
In both arms, if no treatment delay due to neutropenia and/or if no G-CSF administration was required during the first 3 cycles, the first administration of docetaxel or ixabepilone (4^{th} cycle of the sequential regimen) will be performed without any G-CSF support. Conversely, the G-CSF will be maintained during the first cycle of docétaxel or ixabepilone in case of previous delay of treatment due to neutropenia or previous G-CSF administration.

Febrile aplasia *(both arms)*
In case of a fever > 38.5°c occurring during a period of medullar aplasia (neutrophil < 500/mm^3) and having required antibiotherapy or having lasted more than 24 hours, the treatment will be pursued with the same doses, but with addition of G-CSF (Neulasta®) in all remaining cycles of the experimental treatment (both sequences whatever the arm).

In case another febrile aplasia episode occurs despite G-CSF, the doses of the products of the ongoing therapeutic sequence will be decreased by:
- FEC 100: 25%
- Docetaxel: 25%
- Ixabepilone: 20%

in all remaining cycles of the sequence.

6.5.2 Extra-hematological toxicities

Perturbations of hepatic function:
In case of observed Liver biologic abnormalities after FEC Regimen and/or during Ixabepilone or Docetaxel regimen, the Treatment administration will be done according to the following table:

Toxicity	Modification
Transaminases > 1.5 ULN and Alkaline phosphatase > 2.5 ULN	⇨**Decrease the dose of Ixabepilone by 20%** ⇨**Decrease the dose of Docetaxel by 25%**
Total bilirubin > 1 ULN or Transaminases (AST/ALT) > 3.5 ULN and Alkaline phosphatase > 6 ULN	⇨**Stop Treatment (either Docetaxel or Ixabepilone) depends on the arm**

Neurotoxicity

Ixabepilone

In case of a grade 2 neurotoxicity occurring during the ixabepilone sequence, the treatment will be decreased by 20% (32 mg/m²) in all remaining cycles.
In case the grade 2 neurotoxicity is not resolved by decreasing the dose, ixabepilone will be definitively stopped.

Docetaxel

In case of a grade 2 neurotoxicity occurring during the docetaxel sequence, the treatment will be decreased by 25 % (75 mg/m²) in all remaining cycles.
In case the grade 2 neurotoxicity is not resolved by decreasing the dose, docetaxel will be definitively stopped.

Mucositis

Grade 1 or 2 : No dose modification is planned;
Grade 3 and 4 : The dose of Docetaxel and FEC will be decreased by 25% and the dose of Ixabepilone will be decreased by 20% for all the remaining cycles.

Other secondary effects

- For grade 3 toxicities (alopecia and anemia excepted), the treatment must be postponed for at most 2 weeks with respect to the theoretical date until reversion to a grade ≤ 1 is obtained.
- If reversion to a grade ≤1 within a 2 week period is not obtained, the patient is withdrawn from the treatment.
- In case of grade 4 toxicity (alopecia excepted), the patient is withdrawn from the treatment.

No dose modification is planned for **nail and hair disorder**.

All dose reductions for ixabepilone according to toxicity type are summarized in the following table:

Table A: Modifications for ixabepilone

Toxicity	
Platelets ≤ 25 x 10^9/L	decrease dose to 32 mg/m^2
Grade 3 thrombocytopenia with significant bleeding or requiring transfusion	decrease dose to 32 mg/m^2
Any Grade 3 extra hematological toxicity other than neuropathy or arthralgia/myalgia or fatigue	decrease dose to 32 mg/m^2
Grade 2 neuropathy (motor or sensory) resolving to Grade 1	decrease dose to 32 mg/m^2
Grade 3 neuropathy (motor or sensory), and Grade 2 neuropathy not resolving to Grade 1	discontinue ixabepilone

6.6 Retreatment criteria

For both arms, patients may be retreated if ANC ≥ 1,500/mm^3, platelets ≥ 100,000/mm^3 and treatment-related non-hematologic toxicity has resolved to baseline or ≤ Grade 1 (excluding Grade 2 alopecia and Grade 2 fatigue, for which resolution is not required).

If the patient fails to meet criteria for retreatment on Day 22, then retreatment should be delayed and the patient should be re-evaluated at least weekly. See section 6.5 (Dose modifications) if the retreatment delay is due to toxicity. Initiation of subsequent cycles may be delayed for a maximum of two weeks. Any patient who fails to recover from a treatment-related toxicity to baseline or Grade 1 (except Grade 2 alopecia and Grade 2 fatigue) within two weeks of scheduled retreatment will be discontinued from treatment.

6.7 Concomitant Treatments

The prescriptions that are not related to cancer treatment will be noted in the case report form.

6.7.1 Growth factors

G-CSF (filgrastim) must be used in case of febrile neutropenia preventing the therapeutic compliance for all remaining cycles of the therapeutic sequence (see chapter 6.5.1).
The use of prophylactic G-CSF before the second sequence of treatment (C4 to C6) is recommended.
The use of prophylactic G-CSF (primary prophylaxis) is allowed at investigators' discretion and following the institution standard of care.

Growth factor use must be consistent with product label. Growth factor may not be given for 24 hours before or after cytotoxic chemotherapy including ixabepilone.

6.7.2 Hormonal therapy

Hormonal therapy will be prescribed at the end of chemotherapy courses as described in section 6.9 with the following policies:

- each center shall treat all patients homogeneously and following the protocol (refer to section above in which hormonal therapy is described),

- the treatment shall start immediately after chemotherapy or during the year following the end of the treatment by chemotherapy and radiotherapy**.**

6.7.3 Premedications

Recommended premedications for both arms are described in section 6.4.1.

Corticoids will be allowed for use as antiemetics and as premedications before and after the Docetaxel injections.
It will be possible to deliver a treatment with **antiemetics** of the setron family to prevent nausea and vomiting.

Additional Recommended Pre-medication to Prevent Hypersensitivity Reactions if Oral Medication Fails during Ixabepilone courses:

If a patient experiences a hypersensitivity reaction with oral H_1 and H_2 blockers (Regimen 1) then the patient, if re-treated, should be premedicated according to the recommended regimen below:

Regimen 2: Premedicate approximately 30 - 45 minutes prior to each infusion of ixabepilone with:

a) Dexamethasone 20 mg IV (or equivalent),

b) Diphenhydramine 50 mg IV (or equivalent), and

c) Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent).

If a patient continues to experience a hypersensitivity reaction with Regimen 2 then the patient, if retreated, should be premedicated according to the recommended regimen below:

Regimen 3: Premedicate with:

a) Dexamethasone 20 mg po administered, approximately 12 and 6 hours prior to the infusion of ixabepilone,

b) Diphenhydramine 50 mg IV, approximately 30 - 45 minutes prior to each infusion of ixabepilone,

c) Cimetidine 300 mg IV or ranitidine 50 mg IV (or equivalent), approximately 30 - 45 minutes prior to each infusion of ixabepilone.

A suggested approach for retreatment with ixabepilone after a Grade 2 or greater hypersensitivity reaction despite premedication with Regimens 1, 2 or 3 is as follows:[i]

- Dexamethasone 20 mg IV or po (or equivalent) every 6 hours for 4 doses with the last dose administered 30 minutes before rechallenge with ixabepilone.
- With the last dexamethasone dose begin:
  - Diphenhydramine 50 mg IV (or equivalent) 30 minutes before ixabepilone,
  - Cimetidine 300 mg or ranitidine 50 mg IV (or equivalent) 30 minutes before ixabepilone.
- Begin ixabepilone at 25 % of the previous rate for 1 hour.
- Increase rate gradually to complete the total infusion within 6 hours from the time the drug was initially diluted in Lactated Ringer's Injection (LRI) (see Section 6.1).

During each visit, the investigator will record all the information concerning the diseases and concomitant medications.

6.7.4 Prohibited concomitant treatments

Subjects must not continue or institute treatment with the following strong inhibitors of CYP3A4 from 72 hours prior to the initiation of study therapy until end of treatment with ixabepilone or docetaxel: amiodarone, clarithromycin, amprenavir, delavirdine, voriconazole, erythromycin, fluconazole, itraconazole, ketoconazole, indinavir, nelfinavir, ritonavir, and saquinavir.

6.8 Radiotherapy

According to the S.O.R. Breast and the recommendations of the Expert Committee of the SFRO:

- **Breast irradiation** is mandatory in case of conservative breast surgery for all patients.
- After total mastectomy, **chest wall irradiation** is mandatory for pT3-4 and/or ≥ 4N+. It is optional for intermediate risk patients (1-3N+ or pT2, grade III with lymphovascular invasion).
- Irradiation (RT) of **internal mammary and supraclavicular nodes** is mandatory for patients ≥ 4N+. It is optional in patients with 1-3N+ and in pT2N- tumors located in the inner or central quadrants of the breast. If sentinel node biopsy of internal mammary lymph nodes is done systematically, the internal mammary chain RT indication should be done according to the final results of the biopsy and investigator decision.
- Axillary irradiation is not mandatory in case of large axillary node clearance (> or = 8). In case of massive axillary nodes involvement (80 to 100%) or Positive Sentinel Node (not followed by axillary dissection), the participating center should adopt its own policies regarding the benefit/risk ratio for such irradiation.

The same policy and same radiation technique should be adopted by each investigational site for all included patients.

Radiotherapy must begin within 8 weeks after the last cycle of chemotherapy.

The recommended dose is 45 to 50 Gy (1.8 to 2 Gy per fraction – 5 times per week) at the level of the breast, the chest wall and the lymph nodes areas. Equivalent fractions but not less than 4 times per week will be possible. Additional irradiation of the tumoral bed can vary from 10 to 16 Gy (1.8 to 2 Gy per fraction).

6.9 Hormonotherapy

Patients with positive estrogen receptor (ER ≥ 10% in immunohistochemistry) will receive hormonal treatment as indicated bellow:

- Premenopausal women: tamoxifen for 5 years.

- Postmenopausal women: aromatase inhibitors for 5 years, or tamoxifen if aromatase inhibitors are contra-indicated.

- For perimenopausal women (premenopausal status at time of randomization followed by subsequent prolonged amenorrhea after chemotherapy over 1 year): tamoxifen 2/3 years + aromatase inhibitor 2/3 years, or tamoxifen 5 years + aromatase inhibitor 2/3 years. Before the introduction of the aromatase inhibitor (AI), a dosage of FSH and oestradiol levels will be done. The AI will be allowed only if FSH > 30 IU/l and/or oestradiol < 30 ng/l.

The postmenopausal status will be defined as:

- Patient over the age of 60,
- or bilateral oophrectomy,
- or age ≤ 60 with a uterus and amenorrhea for at least 12 months before randomization,
- or age ≤ 60 without a uterus and with FSH>30 IU/l).

7. INCLUSION AND FOLLOW-UP ASSESSMENTS

Patient monitoring from the date of randomization till 5 years after surgery and 5 additional years (long term follow-up) and the patient's assessments' schedule are described in appendix 1.

7.1 Baseline assessment

The patients eligible for the trial and who have signed an informed consent form will undergo initial assessment within 30 days prior to randomization.

However, to include a patient it will be possible to use some examination results performed before enrollment in the trial.

- **Clinical examination**
  Complete clinical examination with weight, height and body surface area determination,
  ECOG performance status (see appendix 2),
  Medical history,
  Concomitant therapies.

- **QlQ C30 / Br23 completion**

- **Radiological examination**
  Within the past year:
  Bilateral mammography,

  Within 3 months prior to the randomization:
  Chest radiography,
  Liver imaging (echography or tomodensitometry),
  Bone scintigraphy (with centered printing plate in case of hyperfixation).

- **Cardiac examination**
  ECG,
  Left VEF assessments by isotopic or echocardiographic method (LVEF assessments must always be done and evaluated with the same method).

- **Hematology and biochemistry examination**
  Hematology: WBC count, platelets count,
  Blood ionogram,
  Hepatic assessment (bilirubin, ALAT, ASAT, alkaline phosphatases),
  Glycemia,
  Calcemia,
  Renal assessment (blood creatinine level, creatinine clearance),
  Pregnancy test,
  FSH assessment for women < 60 years without an uterus and women with HRT.

- **Mandatory histopathological assessment**
  Pathological tumor size, type and EE grade (Scarff-Bloom & Richardson's (SBR) classification as modified by Elston and Ellis),
  Excision quality, margin status,
  Presence of in situ component,
  Presence of lymphatic or vascular emboli,
  Number of excised and invaded lymph nodes,
  Capsular rupture,
  Measurement of estrogen and progesterone receptors (immunohistochemistry only),
  Immunohistochemical determination of cerbB2 expression (FISH or CiSH).

A central review of HR receptors and HER2 status will be performed by reference local pathologists to confirm the eligibility of the patients before randomization. Detailed guidance for central review is given in appendix 3.

- **Sample collection**
  One serum aliquot and one tumor sample will be collected and preserved in liquid nitrogen. See section 11.

7.2 Follow-up assessments during chemotherapy

- **Clinical examination *(Day 21 of each cycle)***
  Complete clinical examination with weight, height and body surface area determination,
  ECOG performance status (see appendix 2),
  Concomitant therapies,
  Toxicities reporting.

- **Hematology and biochemistry examination**
  - **C1 to C3, Day 21**

  Hematology: WBC count, platelets count
  Blood ionogram,
  Glycemia,
  Calcemia,
  Renal assessment (blood creatinine level, creatinine clearance).

  - **C3, Day 21** (*before the first administration of the second sequence of treatment*)

  Hepatic assessment (bilirubin, ALAT, ASAT, alkaline phosphatases)

  - **C4 to C6**

  Day 7:
  Hematology: WBC count, platelets count
  Hepatic assessment (bilirubin, ALAT, ASAT, alkaline phosphatases)
  If abnormal liver tests and a concomitant grade 4 neutropenia are observed, the investigator has to contact the patient and to reassess WBC count every two days until recovery.

  Day 21
  Hematology: WBC count, platelets count
  Blood ionogram,

Hepatic assessment (bilirubin, ALAT, ASAT, alkaline phosphatases)
Glycemia,
Calcemia,
Renal assessment (blood creatinine level, creatinine clearance).

All examinations revealing a treatment-related toxicity must be periodically repeated until toxicity is reverted or until it is assumed irreversible.

- **QIQ C30 / Br23 completion *(Day 21 of cycle 3 and 6)***.

7.3 Assessments at the end of radiotherapy

During the week following the last course of radiotherapy, all patients will undergo the following examinations:

Clinical examination

Complete clinical examination with weight, height and body surface area determination,
ECOG performance status (see appendix 2),
Concomitant therapies,
Toxicities reporting.

7.4 Follow-up visits

After radiotherapy, the patients will be followed:

- every 4 months for the first two years post surgery (Months 12, 16, 20, 24),
- every 6 months for the next three years (Months 30, 36, 42, 48, 54, 60),
- then annually during the 5 years long-term follow-up.

Years 1-2,

- every 4 months: clinical examination and toxicities reporting.
- month 12 (M12) only: LVEF assessment by isotopic or echocardiographic method (LVEF assessments must always be done and evaluated with the same method).
- every year: Mammography. *Other radiological assessments will be done if clinically relevant (Chest X-ray, Hepatic echography, Bone scintigraphy).*

Years 3-5,

- every 6 months: clinical examination and toxicities reporting.
- month 60 (M60) only: LVEF assessment by isotopic or echocardiographic method (LVEF assessments must always be done and evaluated with the same method).
- every year: Mammography. *Other radiological assessments will be done if clinically relevant (Chest X-ray, Hepatic echography, Bone scintigraphy).*

Years 6-10,

- every year: clinical examination, vital status reporting.

8. PREMATURE END OF THE TREATMENT

Study therapy MUST be immediately discontinued for the following reasons:

The treatment can be prematurely stopped for the following reasons:

- toxicity (any clinical adverse event, laboratory abnormality or intercurrent illness which in the opinion of the investigator indicates that continued treatment with study therapy is not in the best interest of the patient,
- pregnancy
- imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness
- disease progression,
- patient's refusal,
- consent withdrawal,
- patient lost to follow-up,
- major protocol violation
- termination of the study by the sponsor.

The same follow up modalities will be applied to patients for whom the treatment is prematurely ended within the limits of what can be reasonably achieved.

9. TRIAL TERMINATION CRITERIA

The trial can be suspended or stopped by the sponsor in consultation with the principal investigator at the request of the competent authority and/or the Committee for the Protection of Persons (CPP) for the following reasons:

- unexpected occurrence or severity of toxicity,
- insufficient patient recruitment,
- poor quality of data collection.

10. EVALUATION CRITERIA

10.1 Main criterion

Disease free survival rate (DFS) at 5 years.

The relapse will be defined as:

- a local or regional relapse,
- a metastatic relapse,
- a contraloteral breast cancer,
- or a death of any cause.

The DFS is 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.

10.2 Secondary criteria

10.2.1 Efficacy

- Distant Metastasis Free Survival (DMFS) rate and Overall Survival rate (OS) for the whole population at 5 years.

- DMFS, DFS and OS at 5 years for triple negative subgroup

- DMFS, DFS and OS at 5 years for the remainder HER2-, PR - , ER+ population

The DMFS is defined as the interval between the date of randomization and the date of the metastatic relapse.

The OS is defined as the interval between the date of randomization and the date of death from any cause.

- Second Neoplasia : Event Free Survival (EFS) will be evaluated both for whole population and subgroups. An Event is defined as a Local Relapse, a Regional Relapse, a Distant Metastasis, an invasive Controlateral Breast cancer, a Neoplasia or a Death from any cause.

The EFS is 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 the date of second neoplasia, or the date of death from any cause, whichever occurs first.

10.2.2 Toxicity

In order to be considered as eligible for toxicity evaluation the patients must have received at least one course of treatment.

The toxicity will be evaluated according to the scale: CTC-AE version 3.0 (see appendix 7).

10.2.3 Quality of life

QlQ C30 / Br23 forms will be completed by the patients before randomization, at the end of third cycle of chemotherapy, and at the end of the last cycle of chemotherapy for both arms. In case of premature end of treatment, a final Questionnary will be completed.

10.2.4 Other criteria

- biology,
- genomics,
- proteomics.

11. Sub-studies

Biology, genomics, proteomics.

This study will collect frozen breast cancer tissue samples and frozen serum samples to analyze them at the RNA and protein levels. The objective is to identify the molecular signatures associated with clinical outcome (metastasis-free survival) in each chemotherapy arm.

- Tumor and serum sample collection

A portion of the resected tumor obtained during initial surgery before treatment will be collected, aliquoted (after cutting off with a scalpel two pieces of the sample, respectively one for the genomic- and one for proteomic study), immediately frozen and stored in liquid nitrogen in the tumor bank of the institution. A pathological control verifying the number of malignant cells in the sample will be done before RNA and protein extraction.
Whenever possible, one serum sample (2.5 ml) will be collected before initiation of the first cycle of chemotherapy. Serum will be immediately processed after collection (within 2 hours) including centrifugation (3000 rpm over 10 minutes), then aliquoted in tubes of 100 to 500 µl rapidly frozen and stored in liquid nitrogen. It is planned to collect a total of 300 patients in each arm.
All samples will be labeled with the institution and patient numbers allocated by UNICANCER.
(see appendix 4).

12. SAMPLE SIZE DETERMINATION AND STATISTICAL ANALYSIS

12.1 Required number of subjects

To show a benefit of 5% in the 5-year DFS (70% in the reference arm versus 75 % in the ixabepilone arm) corresponding to a relative risk of 0.81 (about 20% of relapse risk reduction), 2,500 patients should be enrolled (1,250 patients in each arm) to ensure a power of 80% (beta = 20%) assuming a two-sided situation (Log rank test) and accepting a significance level of 5%.
A minimum of 682 events are to be observed for ensuring a power of more than 80% for detecting the pre-specified 0.81 hazard ratio.

This sample will allow us to show a gain of 6% in 5-year DFS in the triple negative subgroup (corresponding to a relative risk of 0.77 and a relapse risk reduction of 23%) with a power of 80%. This triple-negative subgroup is considered as being equal to two thirds of the whole population (i.e. about 1700 patients).

To avoid any increase of the type one error, the second analysis will be performed only if the difference observed on the whole population (main objective is statistically significant).

Randomization will be stratified based on the following parameters:

- center
- premenopausal status versus postmenopausal status (see definition of menopausal status in section 6.9),
- triple negative tumors versus the remainder of the population.

After the enrollment of the first 300 patients, the hypothesis concerning the proportion of the triple negative subgroup will be verified. If the proportion of triple negative patients is not equal to two thirds of the whole population, the sample size will be re-calculated.

12.2 Statistical analysis

Analysis of the main evaluation criterion will make use of the methodology developed for censored data. The curves of the relapse-free interval and survival curves will be established with the Kaplan-Meïer method.
The efficacy analysis will use the Cox model to estimate the therapeutic effect taking into account a possible unbalanced repartition of the prognosis factors. The relative risks associated to the therapeutic effect will be presented along with their 95% confidence interval. The prognosis factors taken into account in the multivariate analysis will be the following: menopausal status, triple negative tumors, pathological tumor size, lymph node involvement, SBR grading as modified by EE. A sensitivity analysis will also be performed using a stratified logrank test, adjusted on the stratification criteria (except the center).

Statistical analyses will be mainly performed based on the intent-to-treat population for efficacy parameters. Whenever appropriate and necessary, they will be also performed on the eligible patient population or the per-protocol population.

One interim efficacy analysis will be performed 2 years after the recruitment of the last patient. The objective of this interim analysis is to assess whether it is possible to disseminate the results of the study earlier than the final 5-year analysis. This will be possible only in case of overwhelming results in favor of one of the treatment groups. The Peto procedure will be used, considering a p-value less or equal 0.001 to declare the results as positive, in order to keep a type one error close of 0.05 for the final analysis.

Definition of populations:

Intent-to-treat population
All randomized patients will be included in the intent-to-treat population (ITT), whether or not any study medication was administered, and regardless of the eligibility status. As far as statistical inferences are concerned, patients are analyzed in the treatment group and in the stratum to which they were assigned by the randomization.

Eligible population
Eligible patients are patients with no major violations of the inclusion and exclusion criteria. The final decision on patients' eligibility rests with the IDMC that will eventually give a decision on the eligibility of all patients.

Per protocol population
Per-protocol patients are patients with no violation of the major inclusion and exclusion criteria and who received all the 6 cycles of the treatment allocated to by the randomization arm.

Safety population
The safety population will consist of all treated patients, that is, all patients who started at least one infusion of at least one study drug, regardless of their eligibility for the study. Moreover, patients will be analyzed according to the treatment regimen they actually received.

Patients lost to follow-up will be censored at the date of last contact. A patient lost to follow-up is a patient who never came back to the hospital and for whom repeated attempts to contact have failed.
Patients free of disease and not lost to follow-up at the cut-off date for the analysis will be censored at that cut-off date if data exists that documents patient status beyond the cut-off date, or censored at the date of the last visit otherwise.

13. SERIOUS ADVERSE EVENTS

13.1 General definition

It is considered that a serious adverse event (SAE) is any event that:

- leads to the patient's death,
- put the vital prognosis at stake,
- results in an hospitalization or a prolonged hospitalization of the patient,
- induces a permanent invalidity or a severe transient incapacity,
- induces a congenital anomaly, a fetal malformation or an abortion,
- is medically relevant.

The terms *invalidity* and *incapacity* correspond to any clinically relevant physical or psychic handicap, transient or permanent, with impacts on the physical condition/activity and/or the quality of life of the patient.
Any clinical event or laboratory result that is considered as serious by the investigator and that does not correspond to any of the serious adverse event criteria listed above is considered as medically relevant. That which can put the patient at risk and/or require a medical intervention to prevent the development of any serious adverse event previously cited (e.g.: overdosing, a second cancer, pregnancy and new events can be considered medically relevant).

The following events are not considered to be serious adverse events:

- a hospitalization < 24 hours,
- a hospitalization that was programmed prior to the trial's beginning and/or scheduled by the protocol (biopsy, chemotherapy..).

13.2 Definition of an expected serious adverse event (E-SAE)

An E-SAE is a serious event already mentioned in the latest version of the investigator brochure or in the summary of product characteristics (SPC) for the drugs that have been already approved by the CA.

13.3 Definition of unexpected serious adverse event (U-SAE)

A U-SAE is an event that is not mentioned in the investigator brochure or that is differing from the brochure's description due to its nature, intensity or evolution; or that is differing from the summary of product characteristics (SPC) for the drugs with CA approval.

13.4 Intensity criterion

The intensity criterion must not be confused with the seriousness criterion that is utilized to define the obligations of declaration.

The events intensity will be estimated according to the extract from the CTC-AE version 3.0 classification (see appendix 7). The intensity of the adverse events not listed in this classification will be appreciated according to the following scale:

Light (grade 1): does not affect the usual daily activity of the patient;
Moderate (grade 2): perturbs the usual daily activity of the patient;
Serious (grade 3): hampers the usual daily activity of the patient;
Very serious (grade 4): requires reanimation measures / threatens the vital prognosis;
Lethal (grade 5): prematurely ends patient's life.

13.5 Measures to take in the case of a serious adverse event

The investigator informs the pharmacovigilance department of R&D UNICANCER of all serious adverse events, expected (E-SAE) and unexpected (U-SAE), imputable or not to the research process, that might occur during the study or within 30 days following the last treatment administration.

All delayed serious adverse events (that occur more than 30 days after the end of the study) that are reasonably considered to be linked to the protocol's treatment(s) or the ongoing research must be declared without delay.

The SAE declaration must be sent to the pharmacovigilance unit of R&D UNICANCER by FACS within 48 working hours of their observations:

R&D UNICANCER
Pharmacovigilance, France
Tel.: +33.(0)1 44 23 04 16 – Fax: +33.(0)1 44 23 55 70
Email: pv-rd@unicancer.fr

using an **SAE notification form** (cf appendix 6) according to the nature of the event (see Ixabepilone Investigator Brochure and appendix 8 SPC).

For each event, the investigator will note:

- The event's description, as clearly as possible and in accordance with the medical terminology,
- The intensity,
- The date of the event's beginning and end,
- The measures undertaken and whether or not the use of a correcting treatment was necessary,
- If the trial's treatment was interrupted,
- Its evolution will be followed until remission or recovery of the prior state or stabilization of possible sequels,
- The causality between the observed event and the tested treatment or a constraint linked to the research protocol (e.g. a period without treatment, complementary examinations requested within the framework of the research protocol, etc…),
- The causality relating to the drug(s) used in the trial, the treated pathology, another type of pathology, or another treatment. The investigator must also attach a serious adverse event report every time it is applicable:
- A copy of the hospitalization report or of the prolongation of hospitalization,
- A copy of the autopsy report,
- A copy of the results of all complementary examinations, including the relevant negative results and providing the normal laboratory values,
- Any other document that is relevant in the investigator's opinion.

All these documents must be made anonymous.

More information might be requested by the study monitor (by facs or telephone or on a visit to the investigational site).

However, all expected event but that is differing in its intensity, its evolution or its frequency will be considered as unexpected by the pharmacovigilance department.

13.6 SAE follow-up

The investigator is responsible for the appropriate medical follow-up of the patients until the recovery, the stabilization or the death of the patient. **This can indicate that the SAE follow-up is prolonged after the patient has exited the trial.**

The investigator transmits complementary information to the pharmacovigilance cell of R&D UNICANCER using a SAE declaration form and ticks the box: Follow-up **# X**, to specify that it is about a follow-up and not an initial report. She/he sends the form within 48 hours after having obtained the information. She/he also transmits the last follow-up report after reversion to normal or stabilization of the SAE.

The investigator keeps the documents regarding the presumed adverse event to further complement the transmitted information in case of necessity.

She/he answers to the request for complementary information of the PC of R&D UNICANCER to document the initial observation.

14. INDEPENDENT DATA MONITORING COMMITTEE

A trial monitoring committee (IDMC = Independent Data Monitoring Committee) will be set up to ensure: (1) protection of the patients; (2) that the trial is conducted according to the ethics; (3) that the scientific results are reviewed independently during the course and at the end of the trial; and (4) to evaluate the benefit/risk ratio for the trial. This committee has a consultative role with respect to the sponsor. The sponsor takes the final decision regarding the recommendation proposed by the committee.

15. QUALITY INSURANCE AND QUALITY CONTROL

In order to guaranty the authenticity and credibility of the data in accordance with the Good Clinical Practices, the sponsor will set up an insurance quality program that includes:

- management of the trial according to procedures specific to UNICANCER.
- control of the quality of the data provided by the investigation site is performed by the study monitor the role of which is to match and check the consistency of the data reported in the observation handbook with respect to the source-documents,
- possible audit of investigational sites,
- conducting a centralized review covering certain aspects of the protocol (to be specified).

16. DATA PROTECTION AND CONFIDENTIALITY MANAGEMENT

Until the trial results are published, the investigator is responsible for insuring the confidentiality of the totality of the information, handled by herself/himself and all other individuals involved in the course of the trial, that are supplied by UNICANCER. This obligation holds neither for the information that the investigator may communicate to the patients within the context of the trial nor for the already published information.
The investigator commits not to publish, not to spread or use in any manner, directly or indirectly, the scientific and technical information related to the trial.

Nevertheless, in conformity with the article R 5121-13 of the Public Health Code, both the center and the investigator may communicate information relative to the trial:

- to the Health Minister,
- to the public health inspectors who are doctors,
- to the public health inspectors who are pharmacists,
- to the Afssaps General Director and inspectors.

The trial will not be the subject of any written note and/or oral comment without the prior agreement of the sponsor; the totality of the information that is communicated or obtained during the course of the trial belongs in full right to the French Federation of Comprehensive Cancer Centers who can freely use it.

17. PUBLICATION OF RESULTS

All information resulting from this trial is considered to be confidential, at least until appropriate analysis and checking has been completed by the sponsor, the principal investigator and the statistician of the trial.

Any publication, abstract or presentation comprising results from the trial must be submitted for examination and approval to the Sponsor (UNICANCER).

Furthermore, any written communication or presentation must imperatively include a section that mentions UNICANCER, La Ligue Nationale Contre le Cancer (The French League for Treating Cancer) and any institution, investigator, cooperating or collaborating group and scientific society that has contributed to the trial as well as any organism that has financially supported this research.

The first author and writer of the publication will be the principal investigator. She/he may however designate another person to (co-) write the publication.

The other investigators will appear in the list of co-authors in decreasing order, according to the number of recruited patients regardless of the importance of the cooperating group they belong to, followed by a person representing each cooperating group among the investigation centers that have the highest rates of recruitment. The statistician and a sponsor representative will be cited as well.

In an equal manner, publication of the sub-studies (biological studies) will make mention of the name of the person who has carried out the sub-studies as well as the names of all the individuals who have taken part in carrying out these sub-studies.

18. ETHICAL AND REGULATORY ISSUES

The clinical trial must be 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 20th , 1988, relative to the protection of persons participating in biomedical research and modified by the Public Health Law n°2004-806 of August 9th , 2004,

- the law on 'informatics and freedom' (Informatique et Libertés n° 78-17) of January 6th,1978 modified by the law n° 2004-801 of August 6th, 2004 relative to the protection of persons with regard to the computerized processing of personal data,

- bioethic law n° 2004-800 of August 6, 2004.

18.1 Ethic Committee (CPP)

Before starting a biomedical research on human subjects, the sponsor is obliged to submit its project to the opinion of one of the competent committees for the protection of persons where the principal investigator is practicing.

Request of substantial modifications in the initial projects are submitted for the committee's opinion by the sponsor as well.

18.2 Competent authority

Before carrying out or letting a biomedical research to be carried out on its behalf, the sponsor must file a request with the competent authority.
The time necessary to process a demand for authorization shall not exceed 60 days from the date of receipt of the complete file, excepted for products used in cellular therapy and gene therapy for which processing may last 90 days and 120 days respectively. Within 30 days of the receipt of the complete file, the competent authority notifies the sponsor if there exists well-founded objections that prevent the research from being undertaken and informs the committee for the protection of the concerned persons.

18.3 Information and consent of the participants

Prior to carrying out biomedical research on human subjects, a free and written informed consent form must be signed by each individual participating in the trial after she/he has been informed by the investigator during a physician-patient consult and after sufficient time for reflection has been allowed.

Information given to the trial participants must cover all of the elements defined by the public health law of August 9th, 2004 and must be written in a simple and comprehensible patient-appropriate manner.
The French version of the "patient information sheets and informed consents" (PIS/IC) are templates which have to be translated and adapted to local regulatory requirements. In countries where a national coordinating center (NCC) group is identified, the translation and adaptation will be done by this NCC or Group.

However the NCC/G must tell to UNICANCER what the NCC/G has changed and why. This adaptation cannot be validated without the agreement of UNICANCER on the new text.

The final translated and approved local PIS & IC must have a version number and date which must be quoted in all correspondence with local and national ethics committees.

Once the participant is acquainted with the information, she/he must sign all the pages of the information booklet. The original booklet will be kept in the investigator's folder and the duplicate copy will be returned to the participant. **The consent form** must be dated and signed by both the participant in research and the investigator. The original document is archived by the investigator; a copy will be returned to the research participant).

The patient information sheet (PIS) and informed consent form must be associated within the same document to insure that the whole information is given to the research participant.

In the case that the objective of the trial is to carry out genomic or proteomic analysis, the PIS must specify the type of research that will be undertaken and the patient must be given the right to accept or refuse that the biological samples taken from her/him be kept for the purpose of conducting scientific research.

In the case that the trial is conducted on minors, an information booklet appropriate to their comprehension level will have to be written. The authorization to participate in the trial must be issued, in principle, by the two holders of the parental authority. However, the authorization can be given by one holder of the parental authority solely if the other holder cannot give its authorization within a time delay compatible with the methodological requirements inherent to the research process.

18.4 Responsibility of the sponsor

The sponsor of the trial is the natural or moral person that: takes the initiative of conducting biomedical research on human subjects, and is therefore accountable for the research management and for verifying the financing schedule.

The sponsor must be established within the European Community or have one legal representative in an EU member state.

The main sponsor responsibilities are:

- to subscribe a civil-responsibility insurance,

- to register the trial in the European data base and to obtain an **EudraCT** (European Drug Regulatory Authorities Clinical Trials) identification number,

- to request the opinion of the Committee for the Protection of Persons (CPP) on the initial project and the substantial amendments,

- to file the demand of authorization for the initial project and all substantial amendments with the competent authority,

- to provide information on the trial to the heads of the health care centers, the appropriate investigators and the pharmacists,

- to declare to the competent authorities, i.e. the Afssaps and the EMEA (the European pharmacovigilance data bank, Eudravigilance) any suspicion of unexpected serious adverse events (U-SAE) related to any of the treatments used in the trial and communicate the information to the CPP and the investigators of the trial,

- the annual declaration of the security report to the competent authority and the CPP,

- the declaration of the beginning and the end of the trial to the competent authority,

- editing the final report on the trial,

- communicating the information on the trial's results to the competent authority, the CPP and the research participants,

- archiving the trial's essential documents in the sponsor folder for a minimal duration of 15 years after the research is ended.

18.5 Responsibilities of the investigators

The main investigator of each concerned health care center commits to conducting the clinical trial in compliance with the protocol that has been approved by the CPP and the competent authority.

The investigator must not bring any modification to the protocol without having obtained written authorization of the sponsor and the proposed modifications have been authorized by the CPP and the competent authority.

It is the responsibility of the main investigator:

- to provide the sponsor with its own curriculum vitae and co-investigators' curriculum vitas,

- to identify the members of its team that participate in the trial and to define their responsibilities,

- to insure patients recruitment after the sponsor has issued its authorization.

It is the responsibility of each investigator:

- to collect the informed consent form, dated and signed personally by each individual research participant before any selection procedure specific to the trial may start,

- to regularly fill in the case report form (CRF) for each patient included in the trial and to allow the clinical research assistant mandated by the sponsor to have direct access to the source-documents in order to validate the data collected in the observation handbook,

- to date, correct and sign the corrections brought to the CRF for each patient included in the trial,

- to accept regular visits of the study monitor and possibly the auditors mandated by the sponsor or the inspectors of the legal competent authorities.

All documentation relative to the trial (protocol, consent forms, CRF, investigators' folders, etc…) as well as all other original documents (laboratory results, radiographic pictures, reports of physician-patient consultations and clinical examinations, etc…) are confidential material and must be kept in a secured location. The main investigator will be obliged to preserve the data and a list of patient identifications during a minimal period of 15 years after the study has ended.

18.6 Federation of the Patient Committees for Clinical Research in Cancerology

The dedicated task of the Federation of the Patient Committees for Clinical Research in Cancerology (FCPRCC) is to make a second read of the clinical trial protocols in cancerology. The patient committees' federation is coordinated by R&D UNICANCER, a body of UNICANCER. It gathers both the patient committees of the LNCC and other health care centers. It commits to rereading the protocol and proposing improvements dealing principally with the quality of the letter of information to the patients, the setting up of a treatment and monitoring plan, suggesting measures aimed at ameliorating the comfort of the patients.

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Appendix 1 – Flowchart of investigations and study drugs administration

	Baseline	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of radiotherapy	Every 4 months for the first 2 years post surgery (M12, 16, 20, 24)	Every 6 months for the next 3 years (M30, 36, 42, 48, 54, 60) then annually	Every year during 5 years post surgery
		D1	D1	D1	D1	D1	D1				
	Arm 1	FEC	FEC	FEC	Docetaxel	Docetaxel	Docetaxel				
	Arm 2	FEC	FEC	FEC	Ixabepilone	Ixabepilone	Ixabepilone				
Written Informed Consent	x										
Regional Pathological re assessment	x										
Medical history	x										
Concomitant therapies	x	D21	D21	D21	D21	D21	D21	x			
Clinical examination	x	D21	D21	D21	D21	D21	D21	x	x[a]	x[a]	x
ECOG PS	x	D21	D21	D21	D21	D21	D21	x			
Toxicities reporting	x	D21	D21	D21	D21	D21	D21	x	x[a]	x[a]	
Bilateral mammography	x										x
Chest radiography	x										(x[a])
Liver imaging	x										(x[a])
Bone scintigraphy	x										(x[a])
ECG	x										
LVEF assessment	x										M12 and M60
WBC / PLT	x	D21	D21	D21*	D7* + D21*	D7* + D21*	D7* + D21*				
Blood ionogram	x	D21	D21	D21	D21	D21	D21				
Bilirubin, ALAT/ASAT, ALP	x			D21	D7 + D21	D7 + D21	D7 + D21				
Glycemia/ calcemia	x	D21	D21	D21	D21	D21	D21				
Creatinine, creatinine clearance	x	D21	D21	D21	D21	D21	D21				
Pregnancy test – FSH dosage [c]	x										
histology	x										
Serum collection	x										
Frozen and fixed Tumor collection[b]	x										
QIQ C30 / Br23	x			x			x				

[a] in case of suspected recurrence, all necessary imaging will be realized to confirm the diagnosis
[b] frozen sample for participating sites only
[c] for WOCBP treated by HRT and women < 60 years without an uterus
* If abnormal liver tests and a concomitant neutropenia grade 4 are observed, the WBC count has to be monitored every two days until recover

Appendix 2 – ECOG peformance status scale

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

Appendix 3 – Histopathological assessment and Central review

Mandatory histopathological assessment

To ensure as much as possible uniformity in pathological reports, detailed recommendations for management of surgical specimens are listed below. It is recommended to follow these guidelines as much as possible.

– **Pathological tumor size**, as determined by microscopic measurement according to the TNM classification (pT). The largest invasive tumoral focus is measured.

– **Histological type** (ductal, lobular or other type as defined by the 2003 WHO classification of tumours should be specified).

– **Histological grade** according to the Elston & Ellis method (modified Scarff Bloom & Richardson's method).

– This method is based on an assessment of tubule/gland formation, nuclear pleomorphism and mitotic counts (dependent on microscope field area).

Feature		Score
Tubule and gland formation		
Majority of tumour (>75%)		1
Moderate (10-75%)		2
Few (<10%)		3
Nuclear pleomorphism		
Small, regular and uniform		1
Moderate increase in size and variability		2
Marked variation		3
Mitotic count		
Dependent on microscope field area		1-3

Grade I: well differentiated (3-5 points);

Grade II: moderately differentiated (6-7 points);

Grade III: poorly differentiated (8-9 points).

All histological types are to be graded. The histological grade will be re-assessed by the regional referent pathologist (see below).

– **Excision quality**, margin status with measurement of the distance between tumor and the closest margin. If present, margin tumoral involvement should be quantified (focal/extensive).

– **Presence of in situ component**, reported in % of the tumor. The presence of an extensive ductal in situ component should be specified.

– **Presence of lymphatic or vascular emboli** in the peri-tumoral breast tissue.

– **Number of excised and invaded lymph nodes**, capsular rupture if present. In case of sentinel node procedure, the preferred technique is as follows. The sentinel node is cut in half paracentrally, paraffin embedded and then cut in several (at least 3) sections spaced 200µm apart. Sections are stained by hematoxylin and eosin (H&E). Immunohistochemical staining in case of H&E negativity is optional. Frozen section analysis is authorized if necessary

– **Measurement of estrogen (ER) and progesterone receptors (PgR)** (immunohistochemistry only)

– **Immunohistochemical (IHC) determination of HER2** expression and FISH or CISH if necessary (IHC score 2+)

Central review

A central review of hormone receptors (HR) and HER2 status will be performed by referent regional pathologists to confirm the eligibility of the patients before randomization. A representative paraffin block of the tumor will be sent to the closest referent regional pathologist. The immunohistochemical determination of HR (both ER and PgR) and HER2 will be re-performed and reported using the guidelines given below. All regional pathologists participating in this study are members of the GEFPICS (Group for the Evaluation of Immunohistochemical Prognostic Factors in Breast Cancer) and involved in quality assurance programs.

Guidelines for reporting HR and HER2 status

HR (ER and PgR) negative: < 10% immunoreactive tumoral cells

HR (ER and PgR) positive : ≥ 10% immunoreactive tumoral cells

HER2 status reported using the Herceptest® (Dako) scoring system *i.e.:*

Score 0, absence of membranous staining or <10% stained cells

Score 1+, >10% stained cells with a weak and incomplete staining

Score 2+, >10% stained cells with a weak or moderate complete staining

Score 3+, >30% stained cells with a strong and complete staining.

Score 0 and 1+ are reported “negative”.

Score 2+ has to be further assessed by FISH or CISH technique. FISH/CISH-HER2 amplification is defined by a number of HER2 gene copy ≥ 6 or a ratio HER2/centromere 17 > 2,2.

Score 2+ showing HER2 amplification and score 3+ are considered “positive” and are excluded of this study. Score 2+ showing no amplification are considered “negative”.

For all HR and HER2 immunostains, presence of adequate internal (normal glands positive for HR and negative for HER2) and external controls (weak positive cases) will be mandatory.

Appendix 4– Sample collection

For each patient, the following material will be collected:

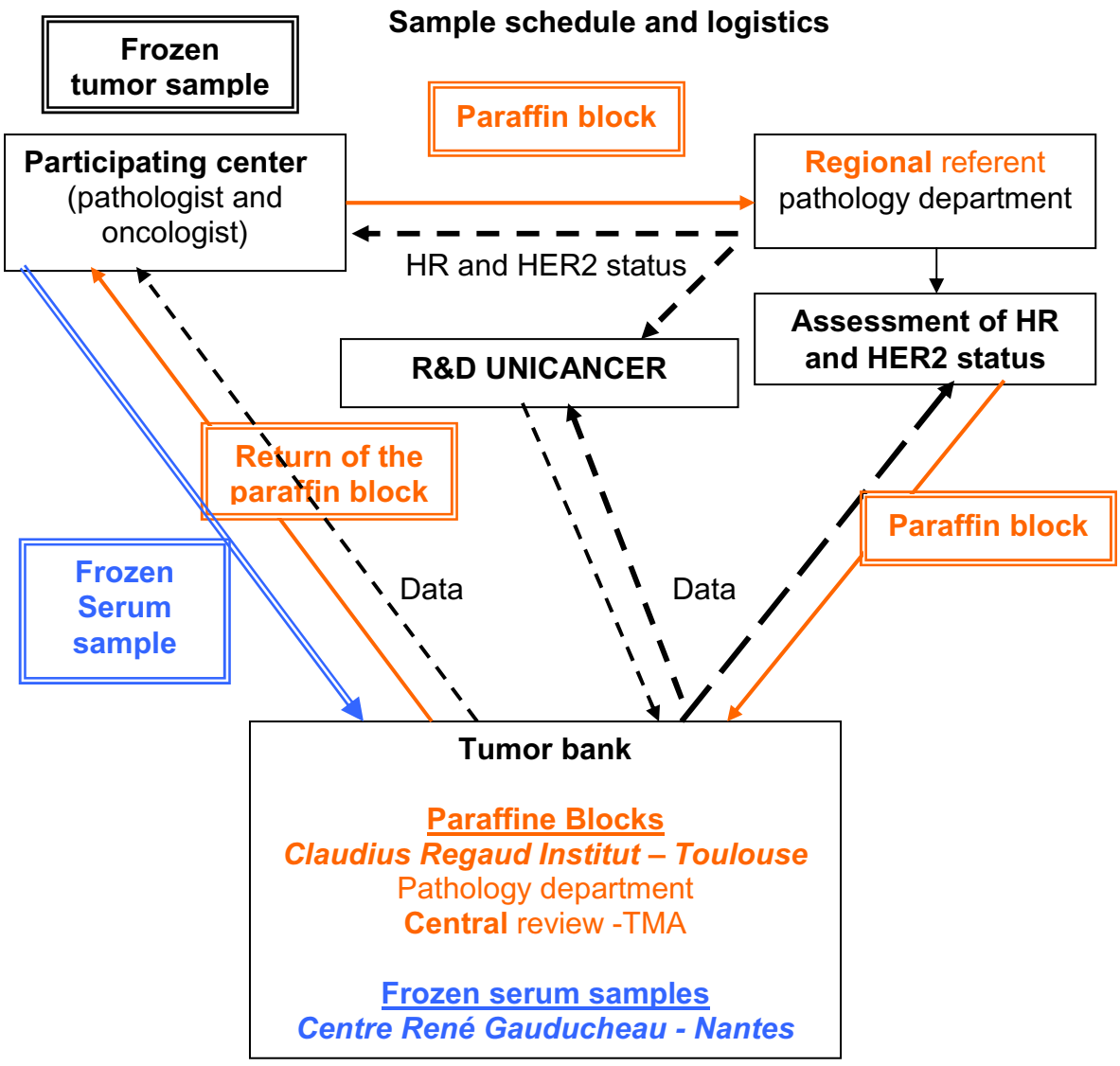
- In order to standardize the histopathological inclusion criteria, **a representative paraffin block** from the tumor will be sent to the regional referent pathologist to i) re-assess the histological grade on H&E stain ii) repeat the HR and HER2 immunohistochemistry. This paraffin block will be then sent to the central pathology laboratory (**Institut Claudius Regaud, Toulouse**) for central pathology review and production of tissue microarrays (TMA). The individual paraffin blocks will be returned to the initial laboratory as soon as the tissue microarray has been made. Rapid (within 7 days after reception of the paraffin block) feedback information of the main standard pathology data will be provided by fax to the local pathologist, oncologist and R&D UNICANCER.

- **one or two frozen tumor sample(s)** will be collected for genomics and proteomics analysis. Immediately after surgery (within 30 minutes), the excised breast specimen must be transported to the pathology department in a dry container without any fixative. The pathologist will take a tissue sample in RNAse-free conditions (i.e. always wearing gloves and using RNAse-free/sterile equipments when processing tissue), from the periphery of the tumor to optimize the chance of a high proportion of malignant cells (>50%) and a good yield of tumor RNA. Tumor tissue samples has to be frozen immediately (within maximum 1 hour of surgery, to avoid RNA degradation) in liquid nitrogen and strored in the tumor bank of the institution. A pathological control verifying the number of malignant cells in the sample will be done before RNA and protein extraction. The availability of the frozen tumor sample will be prospectively registered, and collected by a courier.

- **one blood sample** (2.5 ml) for serum storage will be collected between enrollment and the start of treatment, in order to perform proteomics analysis. Serum will be immediately processed after collection (within 2 hours) including centrifugation (3000 rpm over 10 minutes), then aliquoted in tubes of 100 to 500 µl rapidly frozen and stored in liquid nitrogen.

These samples will be firstly stocked in the biological materials bank of each participating centre, and then shipped on dry ice at the end of the study from each participating center to the proteomics facility **(Centre René Gauducheau, Nantes)**. It is planned to collect a total of 300 patients in each arm.

All samples will be labeled with the institution and patient numbers allocated by UNICANCER. Each patient has to sign the patient information sheet and informed consent form for proteomics and genomics study.



Appendix 5 – Sub-studies

Tissue microarrays

The central pathology review will allow generation of a database of histopathology criteria for all the samples. The tissue microarray will be performed according to the standard technique *i.e.*: determination of representative tumor regions on a H&E stain, punching of three tumor cores and one normal breast core from the paraffin (donor) block to the empty recipient block, cutting of numerous sections and transfer to glass slides, storage at –20°C.

In addition to routine immunostains such as ER, PgR, HER2 and Ki-67, basal phenotype immunostains will be performed using a large panel of markers (Cytokeratins 5/6 and 14, HER1/EGFR, P cadherin, moesin, CD10, etc) described in our previous PACS01 study (Jocelyne Jacquemier). Other markers exploring proliferation/apoptosis and oncogene/antioncogene pathways as previously described will also be analyzed (jocelyne Jacquemier). Specific chemotherapy resistance pathway will be studied according to the most up-dated litterature and in relevance of genomics data provided in this study. CISH (Chromogenic In Situ Hybridization) studies will also be performed on TMA to confirm HER2 status but also to determine HER1/EGFR, c-myc, TOP2A gene copy status.

Proteomics

In order to study post-transciptional gene functions, proteomics analysis of serum and tumor tissue will be performed at the proteomics facility of St Herblain (Nantes). These studies, encompassing different techniques such as SELDI-TOF, MALDI-TOF mass spectrometry and 2D gel electrophoresis, will allow identification of new predictive biomarkers or clinically relevant protein profiles, from serum and tumor tissue. The expression protein profiles will be correlated with tissue histopathology, TMA analysis and clinical outcome.

Genomics

A portion of the excised tumor obtained during initial surgery before treatment will be collected, aliquoted (after cutting off with a scalpel two pieces of the sample, respectively one for the genomics and one for proteomics study), immediately frozen and firstly stored in liquid nitrogen in the tumor bank of the institution. Once every six months, the frozen tumor tissue samples should be shipped on dry ice to the tumor bank of the Claudius Regaud Institute, to collect samples for genomics study. A pathological control verifying the number of malignant cells in the frozen sample will be done before RNA and protein extraction.

If the malignant cell percentage is sufficient (>50%), RNA will be isolated from the samples, and tested for quality using RNA LabChip® (Agilent technologies). RNA expression levels will be measured using microarray technology, in order to determine the overall gene expression pattern. Main objectives are to identify new predictive and prognostic gene expression profiles, but also to validate previously discovered gene profiles. Molecular classification will be performed as previously described in literature, to precisely identify basal-type tumors. Further sub-studies of identified genes involved in basal-like tumors, such as EGFR or p53, will be performed. These studies will encompass several analytical tools. DNA sequencing and new technologies such as array-based Comparative Genomic Hybridization (CGH array), which allows high-throughput, rapid identification and mapping of genomic DNA copy number changes, will be planned to further characterize some previously reported genomic alterations involving the *EGFR* gene in particular.

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Appendix 6 – SAE Form

Notification of A Serious Adverse Event Form

TO BE FAXED TO PHARMACOVIGILANCE - PARIS OFFICE N° + 33 (0)1 44 23 55 70

PROTOCOL N°: EUDRACT N°: COUNTRY :

(DO NOT FULFIL) SPONSOR IDENTIFICATION N° | INVESTIGATOR SITE: N°:

1. PATIENT IDENTIFICATION

INCLUSION N°: |_____| | SURNAME (3 LETTERS): |__|__|__| | 1ST NAME (2 LETTERS): |__|__| | DATE OF BIRTH: |__|__|/|__|__|/|__|__|__|__|

SEX: F ☐ M ☐ | WEIGHT (KG) : |_____| | HEIGHT (CM) : |_____| | TREATMENT ARM : |____|

INITIAL REPORT ☐ | FOLLOW-UP REPORT N° |__|__| | FINAL REPORT ☐

2. INFORMATION ON EVENT

DATE OF ONSET : |__|__|/|__|__|/|__|__| TOXICITY (GRADE NCI – CTC V3) : 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

DIAGNOSIS *OR MAIN SYMPTOMS* :.....

.....

DESCRIBE REACTION AND TREATMENT GIVEN *(INCLUDING RELEVANT TEST/LAB DATA)* :

.....

.....

3. SERIOUSNESS CRITERIA

☐ DEATH ..... DATE |__|__|/|__|__|/|__|__|

☐ LIFE-THREATENING

☐ REQUIRING/PROLONGING HOSPITALIZATION (> 24H) : DATE OF ADMISSION |__|__|/|__|__|/|__|__|

☐ MEDICALLY SIGNIFICANT, SPECIFY : .....

☐ PERSISTENT/SIGNIFICANT DISABILITY/INCAPACITY

☐ OTHER CANCER: .....

☐ CONGENITAL DISORDER/BIRTH DEFECT

4. OUTCOME

☐ ONGOING EVENT

☐ RECOVERED WITHOUT SEQUELA, DATE |__|__|/|__|__|/|__|__|

☐ RECOVERED WITH SEQUELA, DATE |__|__|/|__|__|/|__|__|

SPECIFY SEQUELA: .....

DATE OF END OF HOSPITALIZATION: |__|__|/|__|__|/|__|__|

☐ DEATH RELATED TO THIS EVENT, DATE : |__|__|/|__|__|/|__|__|

☐ DEATH UNRELATED TO THIS EVENT, DATE : |__|__|/|__|__|/|__|__|

☐ UNKNOWN

☐ AUTOPSY YES ☐ NO ☐

5. INVESTIGATIONAL TREATMENT(S)

TREATMENT(S)		DATES		DOSE & UNIT				RELATIONSHIP TO STUDY TREATMENT	
INVESTIGATIONAL TREATMENT (INDICATE THE BRAND NAME OF THE TREATMENT)	ROUTE	DATE OF FIRST ADMINISTRATION (1ST DAY OF 1ST CYCLE)	DATE OF LAST ADMINISTRATION BEFORE SAE	LAST DOSE ADMINISTRATED BEFORE SAE		CUMULATIVE DOSE SINCE THE 1ST ADMINISTRATION		0: EXCLUDED 1: DUBIOUS 2: POSSIBLE 3: LIKELY 4: VERY LIKEY 5: INSUFFICIENT DATA	
				DOSE	UNIT	DOSE	UNIT	INVESTIGATOR	SPONSOR
1.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|
2.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|
3.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|
4.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|
5.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|
6.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|
7.		|__|__|__|__|__|__|	|__|__|__|__|__|__|					|__|	|__|

HAS ONE (OR SEVERAL) TREATMENT(S) BEEN STOPPED?

☐ YES N° |__| N° |__| N° |__| N° |__| N°|__| ☐ NO ☐ NA

DID THE EVENT DISAPPEAR AFTER TREATMENT(S) STOPPED?

☐ YES ☐ NO ☐ NA

HAS ONE (OR SEVERAL) TREATMENT(S) BEEN REINTRODUCED?

☐ YES N° |__| N° |__| N° |__| N° |__| N°|__| ☐ NO ☐ NA

DID THE EVENT REAPPEAR AFTER TREATMENT REINTRODUCTION?

☐ YES ☐ NO ☐ NA

Appendix 6 – SAE Form

Notification of A Serious Adverse Event Form

To be faxed to Pharmacovigilance - Paris office n° + 33 (0)1 44 23 55 70

Protocol N°:	EudraCT N°:	Country :
(Do not fulfil) Sponsor Identification N°	Investigator site:	N°:

1. PATIENT IDENTIFICATION

Inclusion N°: |_____|	Surname (3 letters): |__|__|__|	1st name (2 letters): |__|__|	Date of birth: |__|__| / |__|__| / |__|__|__|__|
Sex: F ☐ M ☐	Weight (kg) : |_____|	Height (cm) : |_____|	Treatment arm : |____|

6. CONCOMITANT DRUG(S) – (exclude those used to treat reaction)

Concomitant Drug	Route	Date started	Date stopped	Ongoing	Indication	Causality Yes	Causality No
1.		From |__|__|__|__|__|__|__|__|	To |__|__|__|__|__|__|__|__|	☐		|__|	|__|
2.		From |__|__|__|__|__|__|__|__|	To |__|__|__|__|__|__|__|__|	☐		|__|	|__|
3.		From |__|__|__|__|__|__|__|__|	To |__|__|__|__|__|__|__|__|	☐		|__|	|__|
4.		From |__|__|__|__|__|__|__|__|	To |__|__|__|__|__|__|__|__|	☐		|__|	|__|
5.		From |__|__|__|__|__|__|__|__|	To |__|__|__|__|__|__|__|__|	☐		|__|	|__|

7. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc…)

8. ASSESSMENT *IN YOUR OPINION, THIS EVENT IS RELATED TO :*

☐ Investigational treatment(s), specify…… ☐ Disease progression

☐ Trial schedule ☐ Concomitant disease(s), specify ……..

☐ Concomitant treatment(s) ☐ Other, specify ……..……

9. Expected Serious Adverse Event	Investigator Yes ☐ No ☐	Sponsor Yes ☐ No ☐
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Investigator Yes ☐ No ☐	Sponsor Yes ☐ No ☐

10. INVESTIGATOR

Reporter's name and function:	Date |__|__| / |__|__| / |__|__|
Address:	Investigator's name:
	Investigator's signature:
Phone: Fax:	
E-mail:	

Appendix 7 – Toxicity criteria (CTCAE)

http://ctep.cancer.gov/

Common Terminology Criteria for Adverse Events v3.0 (CTCAE)
(Publish Date December 12, 2003)

CTCAE v3.0, a new version of the CTEP, NCI CTC v2.0, includes Adverse Events applicable to all oncology clinical trials regardless of chronicity or modality.

Appendix 8 – Products summaries

http://agmed.sante.gouv.fr/
http://www.emea.eu.int/
http://www.vidalpro.net/