PIERRE FABRE MEDICAMENT
Institut de Recherche Pierre Fabre
45, Place Abel Gance
92654 Boulogne-Billancourt

STATISTICAL ANALYSIS PLAN

Compound Number : L00070
Name of Test Drug : I.v Vinflunine (Javlor®)
Study code : L00070 IN 311 B0
Title of the study:

A MULTICENTRE, RANDOMISED, PHASE III STUDY OF VINFLUNINE PLUS CAPECITABINE VERSUS CAPECITABINE ALONE IN PATIENTS WITH ADVANCED BREAST CANCER PREVIOUSLY TREATED WITH AN ANTHRACYCLINE AND A TAXANE

Author Name : **Benjamin POIRIER (Statistician - Axiodis)**

Reviewers Names : **Stéphanie JEAN-ALPHONSE (Head of Statistical Department)**
Mia COMPERNOLLE (Clinical Study Physician – Kelly Life)

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Date of version : **Final version n° 3 (05/07/2017)**
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Reason(s) for change :

- **According to the protocol amendment PA06 (29/07/2016), the statistical analysis was reduced to:**
  - **Efficacy: a descriptive summary of the primary efficacy variable on the ITT population (i.e. no analysis on secondary criteria)**
  - **Safety: a description of safety parameters**

SIGNATURES

	Title	**Name (First & Last name)**	Consistency between SAP and study protocol	**Date**	**Signature**
Author	**Statistician**	Benjamin POIRIER (Axiodis)	**NA**		
Reviewer	**Clinical Study Physician**	Mia COMPERNOLLE (Kelly Life)	**NA**		
Approving Officer	**Head of Statistical Department**	Stéphanie JEAN-ALPHONSE	☐ **Confirmed**		

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LIST OF ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BSA	Body Surface Area
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridisation
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DI	Dose Intensity
EORTC	European Organisation for Research and Treatment of Cancer
FISH	Fluorescent In Situ Hybridisation
FN	Febrile Neutropenia
HB	Haemoglobin
HLGT	High Level Group Term
HLT	High Level Term
i.v	Intravenous
ICH	Immuniohistochemistry
IDMC	Independent Data Monitoring Comitee
IRRC	Independent Response Review Comitee
ITT	Intent-To-Treat
LLT	Lowest Level Term
ORR	Overall Response Rate
OS	Overall Survival
PD	Progression Disease
PDI	Planned Dose Intensity
PLT	Platelets
PR	Partial Response
KPS	Karnofsky Performance Status
MedDRA	Medical Dictionary for Regulatory Activities
PFS	Progression-Free Survival
PT	Preferred Term
PTS	Patients
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	The Statistical Analysis Software
SD	Stable Disease
SGOT	Serum Glutamic Oxalo-acetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIADH	Syndrome of Inappropriate Anti-Diuretic Hormone
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
VFL	Vinflunine
WBC	White Blood Cells
WHO	Work Health Organization
Wk(s)	Week(s)

1. STUDY OBJECTIVES

The primary objective of this study was to compare the progression-free survival (PFS) between the test arm (vinflunine + capecitabine) and the control arm (capecitabine alone) in patients with advanced breast cancer previously treated with an anthracycline and a taxane.

As the final population size is much lower than the population size required to ensure adequate statistical power, the collection of data was stopped and the analyses will be performed when patients have either completed the end of treatment period or completed 35 cycles. As patients are not followed until progression, the results should be not representative and they will only be used as exploratory data. Following the decision to stop the recruitment, the statistical analysis will be actually conducted on the 112 randomised patients and only descriptive analyses will be performed on the ITT population

The primary efficacy analysis will be the description of median PFS in the ITT population.
The Secondary objective of the study is to evaluate the safety that will be described by the treatment arm.

2. STUDY DESIGN

This multicentre, open-label, randomised, Phase III study was designed to enrol 334 patients with advanced breast cancer who have previously been treated with an anthracycline and a taxane. Patients will be randomised in a 1:1 ratio to receive vinflunine plus capecitabine (Arm A) or capecitabine alone (Arm B).

Randomisation was stratified according to the following strata.

1. Karnofsky performance status (“90-100” versus “70-80”),
2. Visceral involvement (yes versus no), visceral lesions include one of the following : liver, lung, pleura (including pleural effusion), heart (including pericardial effusion), peritoneum (including abdominal ascites), spleen and adrenal glands,
3. Study site.

using a minimization procedure (**Pocock, SJ, 1975**) .

Patients randomised in Arm A received:

- **Vinflunine** at the dose of 280 mg/m² on day 1 of each cycle every 3 weeks, over a 20-minute i.v. infusion **and**,

- **Capecitabine** which was self-administered by the patient in an outpatient setting. Patients will take 825 mg/m² twice daily per os for 14 consecutive days beginning on day 1 of each cycle followed by 1 week of rest. A cycle of therapy is defined as 3 weeks.

For patients randomised in Arm B, capecitabine was self-administered by the patient in an outpatient setting. Patients took 1250 mg/m² twice daily per os for 14 consecutive days beginning on day 1 of each cycle followed by 1 week of rest. A cycle of therapy is defined as 3 weeks.

The doses and timing of treatment could be modified based on toxicities experienced by the patient. Dose modifications guidelines are described in Section 5.4 of the protocol.

Patients would continue the study treatment until disease progression, unacceptable toxicity or patient's request.

- Patients showing progressive disease should stop study treatment.
- Patients showing objective response (CR or PR) or stable disease should continue the treatment until progression.

In case of documented progression occurring before the first disease evaluation, the treatment should be discontinued and the response to treatment should be registered as early progression.

After treatment discontinuation, the follow-up period is the time from 30 days after the last study regimen administration or new anticancer treatment start until death.

3. SAMPLE SIZE

The primary objective of the protocol was to show that the vinflunine plus capecitabine test arm is superior to capecitabine as a single agent arm in terms of progression-free survival.

The final analysis will require at least **310 events** (progression or death); this is the number of events needed for a two sided, log-rank test at an alpha = 0.05 significance level and a 80% power to show a statistically significant difference when the true hazard ratio is 0.727 *i.e.*, when the median PFS in the combination arm is 1.5 months greater than median PFS of 4 months in the control arm.

An expected total number of **334 patients** was to be randomised. As the objective of the study could not be achieved, the collection of data was stopped and the analysis will be performed in patients either completing the end of treatment period or patients completing 35 cycles. The statistical analysis will be conducted on the only **112 patients** that have been randomized.

4. EFFICACY PARAMETERS

Tumour assessment will be performed according to the revised RECIST guidelines (**Eisenhauer E, 2009)**. Assessment of all lesions will be carried out at baseline then every 6 weeks (+/- 3 working days) regardless of the timing of the treatment cycles until disease progression.

For patients who discontinued the study treatment before the occurrence of disease progression, clinical and radiological assessments of all lesions will be performed every 6 weeks until disease progression is documented in addition to the survival information. Bone scintigraphy should be performed at baseline and at any time during study in case of suspicion of bone lesions progression due to skeletal related events defined as any observation of the following clinical/biological parameters:

- Pain intensity: increase by at least one grade of the bone related pain using the CTCAE v 3.0 grading:
- Analgesic consumption (per investigator assessment): increase of the analgesic dose by at least 50% or increase of the analgesic level according to the following categories of analgesics: level 1: simple non-opioids analgesic e.g. paracetamol; level 2: weak opioids e.g. codeine or analogs; level 3: strong opioids e.g. morphine.
- Alkaline phosphatase level: increase by at least one grade from baseline or nadir value using the following CTCAE version 3.0 grading.
- Calcaemia: increase by at least one grade from baseline or nadir value using the following CTCAE version 3.0 grading:
- New bone pain symptoms requiring other palliation therapy i.e. radiotherapy, surgery, bisphosphonates.
- Spinal cord compression.
- Pathologic bone fracture.

4.1. PRIMARY EFFICACY PARAMETERS

The primary efficacy parameter is progression-free survival (PFS) according to the investigator. RECIST version 1.1 will be used.

Progression-free survival will be calculated from the date of randomisation until the date of progression or death (whatever the reason of death).

The progression-free survival may be censored at the date of last tumour assessment or the date of last contact of a follow-up showing no progression, whichever occurs last, in the following cases:

- On-going patients
- Lost to Follow-Up
- Consent withdrawn
- New Anti Cancer therapy given
- No post baseline assessment
- Adequate assessment no longer available (i.e. non evaluable tumour)
- No baseline assessment.

4.2. SECONDARY EFFICACY PARAMETERS

Analysis of the following secondary efficacy parameters is no longer applicable in the study:

- the tumour response and disease control rates in both arms,
- the duration of response, the duration of disease control, time to treatment failure and time to first response in both arms,
- the overall survival in both arms.

5. SAFETY PARAMETERS

5.1. ADVERSE EVENTS

Each patient will be assessed for occurrence of adverse events. The CTCAE version 3.0 will be used. Adverse events not classified by the CTCAE will also be reported and graded according to their severity: mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), sudden death (grade 5), not applicable in case of progression or adverse event not gradable according to CTCAE and leading to dose modification (NA).

Treatment Emergent Adverse Event (TEAE) will be considered for analysis of adverse effects. A TEAE is defined as any event that first occurred during the treatment period (i.e. from first drug administration date up to last administration date + 30 days) or that “worsened” during that study period. The definition of “worsening” is described below:

- Any increase in the grade (according to CTCAE) compared to baseline adverse event, or
- Any adverse event becoming serious during the study period, or

- Any adverse event not pre-treated at baseline requiring a corrective treatment during study, or
- Any adverse event requiring a modification of the study drug administration, or
- Any adverse event becoming possibly, probably or definitely related to the study drug

An adverse event that meet one of the criteria described above will be considered as TEAE and reported in the analyses for the reminder of the study, even if the TEAE downgrades to baseline situation.

Baseline situation of the pre-treatment adverse events will be determined by using:

- the worst grade of the adverse event during the pre-study period (within 2 weeks prior to treatment),
- the seriousness of the event during the pre-study period,
- the use of corrective treatment (even if stopped at the day of first administration) during the pre-study period.

This situation will be used as comparator to determine whether an existing adverse event during study period becomes treatment-emergent (i.e. if at least one of these previous parameters gets worst during study treatment).
The adverse events and signs and symptoms will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The implementation of this international terminology in the Oracle Clinical® database will be performed using the avalaible version of MedDRA. Each description of the toxicity (verbatim) will be associated with the five following items:

- System Organ Class (SOC),
- High Level Group Term (HLGT),
- High Level Term (HLT),
- Preferred Term (PT),
- Lowest Level Term (LLT).

The matching of the adverse events reported on the CRF pages with the baseline pre-treatment events to determine the qualification for TEAE will be done by using the Lowest Level Term of the MedDRA dictionary and the qualification for TEAE will be implemented by the study statistician on a dataset provided by the data manager and containing all AEs reported on the CRF pages or derived by the study data manager according to CRF completion guidelines.

Two sets of events will be considered:

- all adverse events regardless of relationship to treatment,
- the adverse events that are possibly, probably or definitely related to treatment,
- If the causality is missing, the AE will be considered as related to study treatment

A cycle will be evaluable for non-haematological toxicity if the following criteria are fulfilled:

- At least one drop or one tablet of any treatment was given,
- The toxicity has been assessed by the investigator during the cycle.

A patient will be evaluable for non-haematological toxicity if at least one cycle is evaluable and will be analysed in the treatment arm she was effectively treated.

5.2. FEBRILE NEUTROPENIA

According to CTCAE version 3.0, febrile neutropenia (FN) is defined as ANC <1.0 x 10^9/L and fever ≥ 38.5°C of unknown origin without clinically or microbiologically documented infection. (§ 5.4.1. "General considerations" of the protocol).

5.3. HAEMATOLOGICAL PARAMETERS

Haematological toxicity will be assessed by laboratory investigations of haemoglobin, WBC, ANC and platelets. Grades will be calculated according to CTCAE version 3.0.

A cycle will be evaluable for haematological toxicity analysis if the following criteria are fulfilled:

- At least one drop or one tablet of any treatment,
- At least one blood cell count between Day 2 and Day 1 of next cycle or end of treatment period for the last administered cycle,
- At least one of the four haematological parameters analyzed has been measured.

A patient is evaluable for haematological toxicity analysis if at least one cycle is evaluable.

5.4. BIOCHEMICAL PARAMETERS

Biochemical toxicity will be assessed by laboratory investigations of liver function tests (i.e. bilirubin, alkaline phosphatase, SGOT/AST, SGPT/ALT), renal function tests (creatinine) and metabolic function tests (sodium, potassium, calcium). Grades will be calculated according to the CTCAE version 3.0.

A cycle will be evaluable for biochemical toxicity analysis if the following criteria are fulfilled:

- At least one drop or one tablet of any treatment has been administered,
- At least one biochemistry test between Day 2 and Day 1 of next cycle or end of treatment period for the last administered cycle,
- At least one of the eight biochemical parameters analysed has been measured.

A patient will be evaluable for biochemical toxicity analysis if at least one cycle is evaluable.

In addition, SGOT/AST, SGPT/ALT and bilirubin will be analyzed acoording to the presence or not of liver lesions at baseline in order to assess the relationship between liver metastasis and worst grade during study.

The same analysis will be done for Alkaline Phosphatase according to the presence or not of liver/bone metastases.

6. OTHER PARAMETERS

6.1. CONCOMITANT MEDICATIONS PARAMETERS

In the same way as the adverse events, concomitant medications will be coded using the specific international terminology WHO-Drug Dictionary version 2007, March 1.

If the start and end dates are both anterior to randomization date will be analysed as prior concomitant medication. Otherwise, the treatment will be considered as concomitant medication.

7. DEFINITION OF POPULATIONS

According to Protocol amendment PA06, all statistical analyses will be performed on the Intent-to-treat (ITT) population. Other populations will not be constituted.

7.1. INTENT-TO-TREAT POPULATION

All randomised patients will be included in the intent-to-treat population. They will be analysed in the arm they were assigned by randomisation.

7.2. ELIGIBLE POPULATION

No longer applicable for the study.

7.3. EVALUABLE POPULATION FOR RESPONSE

No longer applicable for the study.

7.4. EVALUABLE POPULATION FOR SAFETY

All treated patients will be included in the safety analysis. They will be analysed in the treatment arm they actually received.

8. STATISTICAL METHODS

8.1. STATISTICAL SOFTWARE AND METHODOLOGY

Most analyses will be carried out with 9.3 version of SAS® for Windows® (or later version if available). All statistical tests will be two-sided at a 5% level of significance unless specified otherwise.

All baseline descriptive statistics will be presented in summary tables by treatment arm and overall.

Continuous data will be summarized with the following items: frequency, median (if $n \geq 3$), min, max, mean and standard deviation if relevant.

Categorical data will be presented in contingency tables with frequencies and percentages of each modality (including missing data modality).

8.2. STATISTICAL METHODS FOR CATEGORICAL VARIABLES

The χ^2 test will be performed to compare proportions or replaced by Fisher's exact test if the expected frequency in one cell of the contingency table is less than 5. The 95% confidence interval for proportions will be computed following the exact method. If a stratified analysis is required a Cochran-Mantel-Haenszel (CMH) test will be used (option CMH in the TABLES statement of the FREQ procedure in SAS).

8.3. STATISTICAL METHODS FOR ORDINAL VARIABLES

Comparisons between the two treatment arms will be provided for ordinal data using the non-parametric Wilcoxon rank sum test.

8.4. STATISTICAL METHODS FOR CONTINUOUS VARIABLES

The distributions of quantitative data will be examined by the Kolmogorov-Smirnov test in order to test for normality. In case of Gaussian distribution, the comparison between the 2 treatment arms will be made with a Student t-test. If the distribution is not considered as Gaussian then the non-parametric Wilcoxon test will be performed.

8.5. STATISTICAL METHODS FOR TIME DEPENDENT DATA

To describe time dependent parameters, Kaplan-Meier curves and life tables by treatment arm will be provided. Confidence intervals on the median will be calculated using the Brookmeyer and Crowley

method. Hazard ratio and 95% confidence intervals will be reported. A stratified Cox proportional model will be performed to compare the two treatment arms taking into account the stratification factors (except centre) used at the time of randomisation.

9. TREATMENT GROUP DESCRIPTION

9.1. DESCRIPTION AT BASELINE

Analysis of baseline characteristics and demography will be performed on the ITT population, by treatment arm.

9.1.1. Overview of the study

The reasons for treatment discontinuation will be reported. Study discontinuation will be described according to the following reasons: adverse event (related or not), death (related or not), progressive disease, lost to follow up, protocol deviation and other reasons.

The patient status (dead, alive, lost to follow-up) at the cut-off date will be displayed together with each reason of death (progressive disease, adverse event, other).

The number of patients randomised, treated will be presented by treatment group and overall.

Time between randomisation and first administration will be tabulated by treatment arm.

The duration of follow-up is defined as the time elapsed between the date of randomisation and the date of last news or death, death being a censored observation.

9.1.2. Characteristics at baseline

Demographic and baseline characteristics of patients will be displayed. The following variables will be analysed on the ITT population according to the arm assigned at randomisation:

Demographic data

- Age at the time of randomisation
- Categorized groups of age :< 35, [35 – 50[, [50 – 65[, [65 – 75[, [75 – 80[and ≥ 80 years,
- Karnofsky performance status at baseline in categorical data,
- Body weight,
- Body surface area.
- Menopausal status (defined by the presence of the term “Menopause” in the Medical History)

Last available value will be used for baseline analysis.

Stratification data Extract from the IVRS database

- Categorized groups of performance status (“70-80” vs. “90-100”) at randomisation,
- Visceral disease (“yes” vs. “no”) at randomisation.

Disease history:

Characteristics at diagnosis:

- Primary site of cancer: right / left / bilateral
- Histological type: carcinoma / ductal/ lobular /inflammatory/ other (with specification)
- TNM classification,
- SBR grade.

Characteristics at study entry:

- Hormonal receptors at study entry: hormonal receptor ER+/- (positive/negative/unknown or not done), hormonal receptor PR+/- (positive/negative/unknown or not done),
- HER-2 status at study entry (ICH method): 0/1+/2+/3+/missing/not done,
- HER-2 status at study entry (FISH/CISH method): negative/positive/missing/not done,
- Hormone receptors and HER-2 status (triple negative* versus HR positive* and HER-2 negative versus HR positive or negative*),
- Extent of the disease at study entry (locoregional disease/metastatic disease),
- Measurable disease
- Categorized groups of number of organs involved: 1, 2 and ≥ 3 organs,
- Detail of organs involved.
- Time from initial diagnosis to study entry,
- Progression-free interval,
- Categorized groups of progression-free interval: ≤ 4 months / > 4 months,
- Disease-free interval,
- Categorized groups of disease-free interval: ≤12 months / > 12 months
- Treatment free interval,

** : **Triple negative** patients are those presenting with HER2-, PgR- and ER-*
***HR positive** patients are those presenting with PgR+/- and ER+ **or** PgR+ and ER+/-*
***HR negative** patients are those presenting with PgR- and ER-*
***HR positive or negative** patients are those presenting with PgR+/- and ER+/-*

Measurable disease defined as:

- Yes if the number of targeted lesions is > 0,
- No if number of targeted lesions is not > 0 and the number of non-targeted lesions is > 0
- No disease in other cases

The progression free interval is the time interval elapsed between the date of end of the last prior chemotherapy given in the metastatic setting and the date of relapse or progression after this last line of chemotherapy. This progression free interval of patients relapsing or progressing during the last line treatment will be estimated to last one day.

The disease free interval is the time interval elapsed between the date of end of the last prior chemotherapy according to intents neo-adjuvant/adjuvant and the date of relapse or progression.

The treatment free interval is the time elapsed between the date of end of the last treatment (prior chemotherapy, prior hormone therapy…, whichever occurs last) and the first administration of study treatment.

Prior therapy

An overview of prior therapies for Breast carcinoma will be provided giving:

- Number of patients with at least one prior therapy
- Number of patients treated by medication
  - Number of patients treated by chemotherapy
  - Number of patients treated by hormonotherapy
  - Number of patients treated by other antineoplastic drug
- Number of patients who underwent a surgery
- Number of patients who underwent a radiotherapy
- For the last Medication (including chemotherapy, hormone therapy, antineoplastic therapy): intent, time between stop date of medication and date of relapse/progression (expressed in weeks).
- For surgeries: number of surgeries
- For the last radiotherapy: intent

Chemotherapy

- Number of patients who underwent a chemotherapy with intents and intent of last chemotherapy,
- Number of lines,
- Prior anthracycline-based chemotherapy by intent,
- Categorized group of prior cumulative dose of anthracyclines, by type of anthracyclines:

  No Anthracyclines,
  Epirubicin ≥ 300 mg/m²,
  Epirubicin < 300 mg/m²,
  Epirubicin dose unknown,
  Doxorubicin/Pirarubicin ≥ 180 mg/m²,
  Doxorubicin/Pirarubicin < 180 mg/m²,
  Doxorubicin/Pirarubicin dose unknown,
  Epirubicin ≥ 300 mg/m² / Doxorubicin/Pirarubicin ≥ 180 mg/m²,
  Other (Liposomal Doxorubicin).
- Prior taxane-based chemotherapy by intent,
- Categorized group of prior taxanes:

  Docetaxel at any dose,
  Paclitaxel at any dose.
- Class of prior adjuvant/neo-adjuvant chemotherapy (if both in the same time):
  - anthracyclines-based,
    - anthracyclines-taxanes
    - anthracyclines-other
    - anthracyclines single agent
  - taxanes-based,
    - taxanes-anthracyclines,
    - taxanes-other,
    - taxanes single agent, …

- Class of prior advanced disease chemotherapy: anthracyclines-based, anthracyclines-taxanes, anthracyclines-other, anthracyclines single agent, taxanes-based, taxanes-anthracyclines, taxanes-other, taxanes single agent
- Best response of the last chemotherapy by intent and by class of chemotherapy,
- Best response of the last chemotherapy by HER status (0/1+/2+/3+/missing/not done)

Hormone therapy

- Number of patients who underwent a hormone therapy with intents and intent of last hormone therapy,
- Details of hormone therapy treatments received.
- Number of patients who underwent a castration,

Clinical examination

- Electrocardiogram (normal/abnormal but not clinically significant/abnormal clinically significant),
- Temperature, Blood Pressure, Pulse,
- Baseline biological abnormalities,
- Baseline haematological abnormalities.

Last available baseline value will be used for baseline analysis.

Concomitant medications at baseline

- Concomitant medications whatever the intent,
- Concomitant medications with a tumour related intent,
- Concomitant medications with a prophylactic intent,
- Concomitant medications with pre-treatment event indication,
- Concomitant medications with a medical history,

Prior medical history

- Prior medical or surgical history according to MedDRA Preferred Term (PT) and System Organ Classification (SOC).

Pre-treatment events

- Pre-treatment events according to MedDRA Preferred Term (PT) and System Organ Classification (SOC),

9.2. DESCRIPTION DURING THE STUDY

In arm A, a cycle is defined as 1 administration of vinflunine (day 1) and 14 consecutive days (starting from day 1) of capecitabine doses bi-daily with treatment rescheduled every 3 weeks.

In arm B, a cycle is defined as 14 consecutive days of capecitabine doses bi-daily, with treatment rescheduled every 3 weeks.

Duration of exposure is defined as the time elapsed between the date of 1st intake and the date of last capecitabine (if given) administration + 7 days or day 1 (administration of vinflunine) + 21 days if capecitabine not given.

A summary table will provide by treatment arm, the following items:

- Duration of exposure,
- Number of patient with at least one dose permanently discontinued,
- Number of patient with at least one dose temporarily cancelled,
- Number of patients with at least one dose reduced (including dose delayed and reduced),
- Number of patients with at least one dose delayed (including dose delayed and reduced).

The total number of cycles given during the study, the median number of cycles as well as the number of patients by cycle will be given. The categorized groups of vinflunine and capecitabine doses by cycle will be presented.

The actual dose (mg/m²) will be calculated from the total dose administered (mg) divided by the BSA. The BSA will be recalculated at each cycle.

The following categories of vinflunine and capecitabine doses will be used:

Table 9-1 : Categorized dose of vinflunine

Dose category in mg/m²	Dose of vinflunine in mg/m²
>320	] 335 - ∞]
320	] 300 – 335]
280	] 265 - 300]
250	] 237.5 - 265]
225	] 212.5- 237.5]
< 225	] 0 - 212.5]

Table 9-2: Categorized bi-daily dose of capecitabine

Dose category in mg/m²	Dose of capecitabine in mg/m²
Arm A	
> 1250	]1400 – ∞[
1250	]1100–1400]
950	]887.5–1100]
825	] 742.5–887.5]
660	]642.5–742.5]
625	]562.5–642.5]
500	] 437.5–562.5]
<500	] 0–437.5]
Arm B	
> 1250	]1400 – ∞[
1250	] 1100-1400]
950	] 787.5–1100]
625	] 462.5–787.5]
<625	] 0–462.5]

Actual dose intensity (mg/m²/wk) and relative dose intensity (%) will be calculated per cycle and per patient for the vinflunine plus capecitabine and the capecitabine alone arms. Cumulative dose (mg/m²) will also be given. Descriptive statistics such as median and range will be provided.

The number and percentage of cycles/patients with a RDI ≤ 90%, in]90%;100%] or > 100% will also be given.

The actual dose received (mg/m²) at cycle *i* will be equal to the actual dose received (mg) at cycle *i* divided by the body surface area at the beginning of the cycle *i*.

The body surface area will be calculated as follows:

$$\mathrm{BSA} = \frac{\left(W^{**}0.425 \times H^{**}0.725 \times 71.84\right)}{10000}$$

where:

- W = Weight (kg) at the beginning of cycle *i*, or last weight available if missing at cycle *i*,
- H = Height (cm) at the beginning of the study.

BSA as per investigator will be used as an estimate when height has not been provided at baseline.

9.2.1. Actual Dose intensity per cycle

Actual dose intensity per cycle will be defined as follows:

$$\mathrm{DI\ at\ cycle\ i} = \frac{\text{Actual dose recieved (mg/m²) at cycle i}}{\text{Actual duration of cycle i (wk)}} = \frac{\text{Actual dose recieved (mg/m²) at cycle i}}{[(\text{Course date at cycle i}+1)-(\text{Course date at cycle i})]/7}$$

The duration of the last cycle will be estimated to be 3 weeks.

9.2.2. Relative dose intensity per cycle

Relative dose intensity (%) at cycle n° *i* will be the ratio of the actual dose intensity (mg/m²/wk) at cycle *i* to the planned dose intensity (mg/m²/wk) that is to say:

$$\mathrm{RDI\ at\ cycle\ i} = \left(\frac{\mathrm{DI\ at\ cycle\ i}}{\mathrm{PDI}}\right) \times 100 = \left(\frac{\text{Actual dose intensity at cycle i (mg/m²/wk)}}{\text{Planned dose intensity (mg/m²/wk)}}\right) \times 100$$

where :

$$\mathrm{PDI\ at\ cycle\ i} = \frac{\text{Planned dose (mg/m²)}}{\text{Theorical duration of cycle i (wk)}} = \frac{\text{Planned dose (mg/m²)}}{3}$$

Tables 9-3 and 9-4 give for each treatment arm of the study the PDI :

Table 9-3: Planned dose intensity in mg/m²/wk in the vinflunine plus capecitabine arm

Treatment	Administration	Dose (mg/m²)	Planned Dose (mg/m²) per cycle	P.D.I (mg/m²/wk)
vinflunine	Day 1	280	280	93.33
capecitabine	Bid from day 1 to 14	825	23100	7700

Table 9-4: Planned dose intensity in mg/m²/wk in the capecitabine arm

Treatment	Administration	Dose (mg/m²)	Planned Dose (mg/m²) per cycle	P.D.I (mg/m²/wk)
capecitabine	Bid from day 1 to 14	1250	35000	11666.67

9.2.3. Actual Dose intensity per patient

Actual dose intensity per patient will be defined as follows :

$$DI = \frac{\text{Cumulative dose (mg/m²)}}{\text{Treatment duration (wk)}} = \frac{\sum_{i=1}^{n} dose_i}{\sum_{i=1}^{n} duration_i}$$

where :

- $dose_i$ = actual dose received (mg/m²) at cycle *i*,
- $duration_i$ = actual duration (wks) of cycle *i*,
- n = total number of cycle(s) per patient.

9.2.4. Relative dose intensity per patient

Relative dose intensity (%) will be the ratio of the actual dose intensity (mg/m²/wk) to the planned dose intensity (mg/m²/wk) that is to say :

$$RDI = \left(\frac{DI}{PDI}\right) \times 100 = \left(\frac{\text{Actual dose intensity (mg/m²/wk)}}{\text{Planned dose intensity (mg/m²/wk)}}\right) \times 100$$

where :

$$PDI = \frac{\text{Planned dose (mg/m²)} \times \text{number of cycles}}{\text{Theorical duration of a cycle (wk)} \times \text{number of cycles}} = \frac{\text{Planned dose (mg/m²)}}{3}$$

9.2.5. Dose reductions

Dose reductions are allowed by the study protocol for vinflunine and capecitabine in both arms. The number of patients and cycles with a dose reduction will be presented as well as the reasons.

9.2.5.1. Vinflunine dose reduction at day 1 (Arm A)

- Number of patients with at least one dose of vinflunine in arm A reduced at day 1

- Number of cycles with a dose of vinflunine in arm A reduced at day 1

- Reasons for vinflunine dose reduction at day 1 (as per protocol):

Reason for dose reduction of vinflunine	Dose reduction as per protocol				N cycles	
	From 280 to 250 mg/m²		From 250 to 225 mg/m²			
	N	%	N	%	N	%
Non-study drug related adverse event Study drug related haematological AE Study drug related non-haematological AE Other						

- Total number of haematological and non-haematological toxicities and nature, as per protocol or not, which have led to a dose reduction,
- Detail of the haematological and non-haematological toxicities which have led to a dose reduction,

9.2.5.2. Capecitabine dose reductions

- Number of patients with at least one dose of capecitabine reduced:

- Number of cycles with at least dose of capecitabine reduced:

- Reasons for capecitabine dose reductions (as per protocol)
- Total number of haematological and non-haematological toxicities, which have led to a dose reduction of capecitabine,
- Detail of the haematological and non-haematological toxicities which have led to a dose reduction of capecitabine,

9.2.6. Treatment cancellation (Capecitabine)

Capecitabine dosing may be cancelled as per protocol (§ 5.4.3.2 of the protocol).

The number of cycles with at least one day (morning and afternoon doses both not taken for capecitabine) cancelled and number of patients with at least one day of dosing cancelled will also be displayed. Reasons for treatment cancellation will be provided.

- Number of patients with at least one capecitabine dose cancelled,
- Number of cycles with at least one capecitabine dose cancelled,
- Reasons for capecitabine dose cancellation.
- Total number of toxicities, as per protocol or not, which have led to a capecitabine dose cancellation,
- Detail of the haematological and non-haematological toxicities which have led to a capecitabine dose cancellation,

9.2.7. Vinflunine infusion interruption (Arm A)

Vinflunine infusion interruption may occur. The number of patients and cycles with a infusion interruption will be presented as well as the reasons.

- Number of patients with at least infusion of vinflunine in arm A interrupted at day 1,
- Number of cycles with a infusion of vinflunine in arm A interrupted at day 1,
- Reasons for vinflunine infusion interruption at day 1,
- Total number of toxicities, as per protocol or not, which have led to a infusion interruption,
- Detail of the haematological and non-haematological toxicities which have led to a infusion interruption,

9.2.8. Treatment delay

The number of patients and cycles delayed will be presented with reason for treatment delay.

A treatment cycle will be considered as delayed if administered $\geq$ 4 days after the planned date with a three weeks interval from day 1 of previous cycle. In arm A, the date of vinflunine administration will determine the day 1 of the cycle; in arm B (and for patients continuing capecitabine alone in arm A), the first day of capecitabine intake will determine the day 1 of the cycle, whatever the first dose has been taken in the morning or the afternoon. Only delay for Day 1 will be calculated.

The delays will be categorized as follows:

- [4 – 7 days[,
- [7 – 14 days[,
- $\geq$ 14 days.

The following parameters will be described by arm:

- Number of patients with at least one cycle delayed by four days or more,
- Number of cycles delayed,
- Categorized groups of cycle delay,

- Reasons for cycle delay of four days or more,
- Total number of haematological and non-haematological toxicities, and nature, as per protocol or not, which have led to a dose delay,
- Detail of the haematological and non-haematological toxicities which have led to a delay,

9.2.9. Route of administration and setting

The route of vinflunine administration and setting in arm A will be presented by patient and by cycle.

- Route of administration and setting by patient and by treatment arm:

	Arm A	
	N	%
Route of administration Central venous line Peripheral vein		
Change in route of administration No Yes		
Setting Out-patient clinic In-patient clinic		
Change in setting No Yes		
Number of patients		

- Route of administration by cycle:

Courses	Arm A	
	Central venous line N (%)	Peripheral vein N (%)
1 **2** **3** **4** **5** **6** **…**		
Number of cycles		

9.2.10. Concomitant medications

Medications administered concomitantly with the study treatment will be summarized according to the prophylactic indication, tumour related indication, pre-treatment events or medical history indication and whatever the indication, by patient and by cycle.

10. EFFICACY ANALYSES

10.1. PRIMARY EFFICACY ANALYSIS

The primary efficacy population will be the intent-to-treat (ITT) population.

As the final population size is much lower than the population size required to ensure adequate statistical power, no statistical test will be performed.

PFS will be described by treatment arm. Hazard ratio and 95% confidence interval of the hazard ratio will be computed using the SAS® procedure «PHREG». The treatment arm will be entered as a covariate in the Cox proportional hazard model and the variables of stratification at randomisation (except centre) will be entered as stratification factors in the model. Kaplan-Meier curves will also be provided by treatment arm.

10.2. SENSITIVITY ANALYSES OF THE PRIMARY EFFICACY PARAMETER

No sensitivity analyses of the primary efficacy parameter will be performed.

10.3. SECONDARY EFFICACY ANALYSES

Not Applicable.

11. SAFETY ANALYSES

Safety analysis will be performed on the evaluable population for safety described in section 7.4 for each treatment arm.

11.1. OVERVIEW OF THE SAFETY

The adverse events incidence, overall and per CTCAE grade, will be presented. The worst CTCAE grades or maximum severity grades (for non haematological adverse events not classified by the CTCAE) will be analysed by cycle and by patient, and by treatment arm, regardless or not to the relationship to treatment.

For definition of evaluable cycle/patient for non-haematological and haematological toxicity, see § 5.1 and § 5.3, respectively.

Some laboratory toxicities will be presented when reported as adverse events according to the study completion guidelines.

Listings of adverse events not graded and those one occurring during follow up will be provided. The pre-treatment events will also be presented.

11.2. ADVERSE EVENTS

11.2.1. All adverse events

The incidences of the treatment-emergent adverse events (TEAE) as defined in 5.1, graded according to NCI-CTCAE version 3.0 will be presented using the MedDRA SOC and PT defined during the MedDRA coding process.

A summary table will provide by treatment arm the following:

- On treatment deaths
- Patients with at least one AE
- Patients with at least one TEAE (overall and by grade)
- Patients with at least on SAE
- Patients with at least one TEAE leading to discontinuation
- Patients with at least one TEAE requiring dose interruption and/or adjustment
  - Patients with at least one TEAE requiring dose interruption
  - Patients with at least one TEAE requiring dose adjustment
- Patients with at least one TEAE requiring additional therapy
- Cycles with at least one AE
- Cycles with at least one TEAE (overall and by grade)

Overall incidences per patient and per cycle will be depicted as well as the incidence of non related and related toxicities only. An analysis will also present the CTCAE grade presented for each SOC and PT per patient and cycle according to the relationship with study treatment.

11.2.2. Serious adverse events

The number of patients with at least one SAE, one related (suspected and insufficiently documented) SAE, number of SAEs, number of related SAEs will be tabulated. Incidences of SAEs by SOC and PT will be presented according to the relationship with study treatment.

A listing of the serious adverse events will be also provided with the following variables: patient number, cycle number, seriousness, CTCAE grade, date of onset, date ceased, action taken with study drug, corrective treatment and causality

11.2.3. Deaths

The number and percent of patients dead will be tabulated by treatment arm, including number and percent of dead related to AE/SAE, due to progression or other reasons.

A listing of the deaths within 30 days after last administration or more than 30 days after last administration will be provided with the following variables: patient number, cycle number, date of death, reason of death, source of information.

11.3. LABORATORY TESTS

11.3.1. Haematological toxicities

Leukocytes, ANC, haemoglobin and platelets data will be analysed for haematological toxicity.

A first analysis will present the worst grade (overall / grade 3/4) by patient and the worst grade (overall / grade 3/4) experienced during a cycle. In a second analysis, the worst grade of patients according to the grade at baseline will be tabulated.

11.3.2. Biochemical toxicities

Liver, renal and metabolic function tests will be analysed with a focus on bilirubin, alkaline phosphatase, SGOT/AST and SGPT/ALT, creatinine, creatinine clearance, sodium, potassium and calcium.

In order to examine the evolution of biochemical toxicities, worst CTCAE grade (hypo and hyper for metabolic function tests) will be analysed in relation to the grade presented by the patient at baseline.

In addition, the relationship between liver involvement at baseline and the worst CTCAE grade during study will be studied for SGOT/AST, SGPT/ALT and bilirubin. The same analysis will be done for the worst CTCAE grade of alkaline phosphatase and liver and/or bone metastases at baseline.

A listing of patients having at least one LDH>IU/L, giving treatment arm, all LDH values and the visceral status at randomisation will be provided.

12. CHANGES INTERFERED SINCE LAST VERSION

According to the protocol amendment PA06 (29/07/2016), the statistical analysis was reduced to:

- Efficacy: a descriptive summary of the primary efficacy variable (PFS) on the ITT population (i.e. no analysis on secondary criteria),
- Safety: a description of safety parameters.

As a consequence, the following analyses have been deleted:

- Adverse events of special interest and specific analysis of constipation, because exhaustive tables of AE will be produced,
- Description over time of values and changes from baseline for laboratory date, because CTCAE grades will be provided,
- Some detailed tables of disease history, prior therapies and concomitant medications, limiting the analyses to an overview of the safety and patients characteristics.

Summary tables of adverse events, prior therapies for breast carcinoma and exposure have been added. Analyses of laboratory values have been specified, such as LBH or Creatinine Clearance.

All data will be provided in individual data listings in appendix 16.2 of the Clinical Study Report.

13. REFERENCES

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14. APPENDIX 1: LIST OF TABLES, FIGURES AND LISTINGS

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15. APPENDIX 2: STATISTICAL ANALYSIS CONVENTIONS

15.1. CALCULATION OF A DURATION

Duration in years or months (i.e. treatment duration, follow-up time, disease and treatment free intervals, time from diagnosis to study entry, time to first response, duration of response, stabilisation and disease control, PFS and overall survival) will be calculated as follows :

$$\text{Duration (in months)} = \frac{(\text{Date 2 - Date 1}) + 1}{30.4375}$$

with Date 2 $\geq$ Date 1.

$$\text{Duration (in years)} = \frac{(\text{Date 2 - Date 1}) + 1}{365.25}$$

For example, age of the patients will be calculated as follows :

$$\text{Age (in years)} = \frac{(\text{Date of registration - Date of birth}) + 1}{365.25}$$

15.2. CALCULATION OF A DELAY

Delays, usually in days, (i.e. number of days of delay in a cycle, delay between randomisation and first administration, number of days between last administration or visit and death, delay between diagnosis and study entry, delay between diagnosis and progression, time from randomisation to first concomitant radiotherapy) will be calculated as follows :

$$\text{Delay (in days)} = \text{Date 2 - Date 1}$$

with Date 2 $\geq$ Date 1.

15.3. MISSING DATA

15.3.1. General conventions

Following internal biometry conventions are used:

- “A” stands for a non-applicable information,
- “M” stands for an information not present on CRF form,
- “D” is indicating that the mention “Not done” was ticked on the page,
- “O” is a code for a date ongoing,
- “K” is an abbreviations for unknown information.

15.3.2. Conventions for dates

For dates, if the day is missing then convention is to put the day to the value of 15 (half of the month). If the day and the month are missing then convention is to put the day to the value of 01 and the month to the value of 07 (half of the year). This convention allows to approximate some delays (mostly delays analysed at baseline).

15.4. DOSE MODIFICATIONS

Dose modifications will be determined between two subsequent cycles. Variation will be calculated by comparing actual dose received.

15.5. OVERALL RESPONSE OF THE PATIENT

According to the revised RECIST, no confirmation of the response will be required in this phase III study to qualify the patient as CR or PR.

15.6. DATE OF FIRST RESPONSE AND DATE OF PROGRESSION

15.6.1. Date of first response

The date of first response is the first date where CR, or PR is assessed. It can be found in the CTA module of the CRF. If for the same tumour evaluation, the assessments where made at different dates, the maximum of all the dates of assessment of the cycle will be taken into account.

15.6.2. Date of progression or death

The date of progression is the first date where PD is assessed. The date used for PFS calculation will be the date of progression or the date of death. Date of first progression or death can be found:

- In CTA module of the CRF,
- In ETA module of the CRF (in case of assessment during the follow-up, i.e. after the end of the treatment period),
- In DRF module of the CRF in case of death without “objective” progression assessed before.

If for a tumour evaluation, several assessments show a PD at different dates and the global response of the cycle is PD, the minimum of all the dates of assessment of the cycle showing PD (including appearance of new lesions) will be taken into account.

15.7. TOXICITY

15.7.1. Haematological toxicities

The following units for HGB, WBC, PLT and ANC will be used for the analysis of haematological toxicity :

Parameters	Units
HGB	g/L
WBC	10^9/L
PLT	10^9/L
ANC	10^9/L

If values were expressed in different units in the CRF, the data management department will be in charge of the conversion to SI units.

Calculation of grades will be done using the following boundaries :

Grade	HGB	WBC	PLT	ANC
Grade 0	]200 – 120]	]15 – 4]	]500 – 150]	]10 – 2]
Grade 1	]120 – 100]	]4 – 3]	]150 – 75]	]2 – 1.5]
Grade 2	]100 – 80]	]3 – 2]	]75 – 50]	]1.5 – 1]
Grade 3	]80 – 65]	]2 – 1]	]50 – 25]	]1 – 0.5]
Grade 4	< 65	< 1	< 25	< 0.5

Of note, the study data manager calculates grades of haematological toxicities before database is made available to the study statistician on a read-only basis.

15.7.2. Biochemical toxicities

The following units for SGOT/SGPT, bilirubin, alkaline phosphatase and creatinine will be used for the analysis of biochemical toxicity :

Parameters	Units
SGOT/SGPT	IU/l
Bilirubin	µmol/l
Alkaline phosphatase	IU/l
Creatinine	µmol/l

If values were expressed in different units in the CRF, the data management department will be in charge of the conversion to SI units.

Calculation of grades will be done using the following boundaries:

Grade	SGOT/SGPT	Bilirubin	Alkaline phosphate	Creatinine
Grade 0	[LLN – UNL]	[LLN – UNL]	[LLN – UNL]	[LLN – UNL]
Grade 1	]UNL – 2.5 x UNL]	]UNL – 1.5 x UNL]	]UNL – 2.5 x UNL]	]UNL – 1.5 x UNL]
Grade 2	]2.5 – 5 x UNL]	]1.5 – 3 x UNL]	]2.5 – 5 x UNL]	]1.5 – 3 x UNL]
Grade 3	]5 – 20 x UNL]	]3 – 10 x UNL]	]5 – 20 x UNL]	]3 – 6 x UNL]
Grade 4	> 20 x UNL	> 10 x UNL	> 20 x UNL	> 6 x UNL

Of note, the study data manager calculates grades of biochemical toxicities before database is made available to the study statistician on a read-only basis.

For creatinine clearance, the worst values will be analysed according to the following classes: <50ml/mn or ≥50ml/mn.

15.7.3. Definition of a toxic death

A toxic death is defined as a death caused by a related adverse event either during the treatment period or in the 30 days following the last administration.

15.7.4. Treatment duration

Treatment duration is calculated for each patient from the date of randomisation to the date of last day 1 administration + 21 days.

15.8. END OF STUDY

15.8.1. Death for progression

In case of death for progression (so PD documented in the tumour assessment form and death documented in death report form are at the same date), the reason for treatment discontinuation is **Progression**.