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STUDY: L00070 IN 309 F0

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L0070 / IV vinflunine

A phase III study of IV vinflunine in combination with methotrexate versus methotrexate alone in patients with recurrent or metastatic squamous cell carcinoma of the head and neck previously treated with platinum-based chemotherapy

Pierre Fabre Study Code: L00070 IN 309 F0

EudraCT number: 2011-005081-38

Sponsor's representatives:

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Version No.: 7 Date: 5th February 2016

STUDY SYNOPSIS

NAME OF SPONSOR:	**PIERRE FABRE MEDICAMENT**
NAME OF FINISHED PRODUCT:	**JAVLOR®**
NAME OF ACTIVE SUBSTANCE(S):	VINFLUNINE DITARTRATE

Title of the study: Phase III study of IV vinflunine in combination with methotrexate versus methotrexate alone in patients with recurrent or metastatic squamous cell carcinoma of the head and neck previously treated with platinum-based chemotherapy (study L00070 IN 309 F0)

Planned list of investigators: 117 out of 150 planned centers have been active in Austria, Belarus, Belgium, Brazil, Estonia, France, Germany, Italy, Mexico, Poland, Russia, Slovakia, Spain, Taiwan and Ukraine

Study rationale:

For patients with incurable recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN), platinum-based chemotherapy is frequently the only available treatment. Recently the addition of cetuximab was shown to improve overall survival over platinum-based chemotherapy alone in this setting (Vermorken JB, 2008). However recurrent/metastatic SCCHN remains incurable and all patients eventually relapse/progress. Second-line therapy options are scarce and single-agent methotrexate is still the standard treatment.
Vinorelbine proved to be an active drug in SCCHN patients having failed prior platinum-based chemotherapy (Testolin A., 1994 ; Porta C., 2001). Vinflunine (VFL) is a novel generation vinca-alkaloid which has been granted a marketing authorization approval for the second-line treatment of transitional cell carcinoma of the urothelial tract after platinum failure by the EMA. Moreover VFL was shown to be effective in the second line treatment of non-small cell lung cancer after platinum failure and in metastatic breast cancer after anthracycline and taxane failure. Therefore IV vinflunine is a promising candidate in SCCHN patients after platinum failure.
Single-agent methotrexate remains the standard second-line treatment although its efficacy is poor. Methotrexate has been successfully combined with vinca-alkaloids for the treatment of a variety of solid tumours including bladder cancer (Harker W.G., 1985), breast cancer (Elomaa J., 2003), mesothelioma (Hunt K., 1996) and SCCHN (Iop A., 1998).
Recent preliminary phase I results of the vinflunine plus methotrexate combination in SCCHN (L00070IN117F0), based on a clinical review, show encouraging antitumour activity and an acceptable safety profile (Preliminary Clinical Evaluation). Based on these premises, the combination of vinflunine and methotrexate is expected to improve on methotrexate monotherapy.

Study period (estimated): Q1 2014-Q4 2016	**Clinical phase: III**

Objectives:

- primary : to compare the overall survival (OS) of IV vinflunine in combination with methotrexate versus methotrexate alone in incurable recurrent / metastatic SCCHN patients who have failed platinum-based chemotherapy.

- secondary : . to evaluate the response and disease control rate in the 2 study arms
  . to assess the response and disease control duration in the 2 study arms
  . to assess the progression-free survival in the 2 study arms
  . to assess the safety profile in both arms
  . to compare the change in disease-related symptoms in the 2 study arms by using the EORTC quality of life questionnaire

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Methodology

This is a multicenter, open-label, randomised phase III study of IV VFL in combination with methotrexate versus methotrexate alone in incurable recurrent / metastatic SCCHN patients previously treated with platinum-based chemotherapy.

Patients will be stratified at inclusion by the following factors :
- WHO performance status (PS) (0 versus 1)
- Refractory or resistant to platinum versus other
- Prior radiotherapy (yes versus no)
- Prior treatment with any anti-EGFR medication (yes versus no)
- Center

Patients will be randomly assigned to receive in a 1 : 1 ratio one of the two study treatments :
- Arm A : vinflunine given at the dose of 280 mg/m² on day 1 and methotrexate administered at the dose of 30 mg/m² on days 1 and 8 every 3 weeks.
- Arm B : methotrexate given at the dose of 40 mg/m²/week.

An Independent Data Monitoring Committee (IDMC) will be charged with reviewing all the safety and efficacy data.

An early safety review will be conducted after 40 patients are randomised (20 in each arm) and treated for at least one cycle. The IDMC will review the safety data and make recommendations accordingly.

An interim analysis of efficacy and safety will be performed after the first tumour assessments scheduled at 6 weeks from the first 100 patients randomised in the test arm become available. The non progression rate at 6 weeks and the safety in the test arm will be reviewed by the IDMC. Based on this interim analysis, the IDMC will determine whether the enrolment should continue or not. Because the projected accrual could be slow in the study, the patient enrolment will continue while waiting the decision of the IDMC.

Following this interim analysis, a futility analysis has been carried out.

The results of this analysis showed that the probability to demonstrate a significant benefit of overall survival at the time of the final analysis is very low.

As a consequence, the sponsor has decided to stop the recruitment of study patients on 16th October 2015.

Number of patients

A sample size 530 randomised patients (265 randomised patients per arm) was planned, including an anticipated 5% loss to follow-up.

A total of 459 patients (230 randomised patients in the arm A and 229 randomised patients in the arm B) have been enrolled in this study. The inclusions are now closed.

Diagnosis and main inclusion criteria

Inclusion criteria :
Patients must satisfy all the following inclusion criteria before they are allowed to participate in the study:

1. Patients must give written informed consent (personally signed and dated) before completing any study-related procedure

2. Histologically or cytologically confirmed recurrent and/or metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx

3. Documented progressive disease after chemotherapy for locoregionally advanced or recurrent/metastatic SCCHN which included a platinum derivative (cisplatin or carboplatin) that is not suitable for local therapy. Platinum-based chemotherapy can have been associated with cetuximab.
Eligible patients include one of the following categories :
- patients who have received induction chemotherapy (ICT) consisting of cisplatin plus 5-fluorouracil or docetaxel plus cisplatin plus 5-fluorouracil followed by radiotherapy alone or chemoradiation (CRT) or radiotherapy concomitant with cetuximab provided that recurrence occurs within 6 months of completing local therapy
- patients who have completed cisplatin-based CRT with or without ICT provided that recurrence occurs within 6 months of completing local therapy. The minimum cumulative dose of cisplatin during CRT must be 200 mg/m².
- patients with recurrent and/or metastatic SCCHN who relapse after platinum-based (cisplatin or carboplatin) chemotherapy given in first-line with an interval < 12 months

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Diagnosis and main inclusion criteria (ctd)

- patients with metastatic SCCHN at diagnosis who have been treated with platinum-based (cisplatin or carboplatin) chemotherapy in first-line and relapse with an interval < 12 months.

The definition of failure will be as follows :

- refractory disease : progression during platinum-based regimen
- resistant disease : progression during the time from completion of platinum-based chemotherapy but less than 6 months after its completion
- other type of failure : progression ≥ 6 months but < 12 months after completion of platinum-based chemotherapy

4. No more than one prior chemotherapy regimen for recurrent/metastatic disease. Prior treatments with targeted therapy used in monotherapy are allowed

5. Minimum interval of 4 weeks between the completion of first-line chemotherapy and randomisation

6. Measurable or non measurable disease

7. WHO performance status ≤ 1

8. Age ≥ 18 years and < 80 years

9. Adequate haematological function: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, haemoglobin ≥ 10g/dL.

10. Adequate hepatic function: transaminases ≤ 2.5 x Upper Limit of Normal (ULN), total bilirubin ≤ 1.5 x ULN, alkaline phosphatase ≤ 5 x ULN

11. Adequate renal function: a calculated (Cockroft-Gault) creatinine clearance > 60 ml/min

12. Women of childbearing potential must be using a medically accepted method of contraception (barrier methods, oral contraceptive, intrauterine devices) to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and for up to 3 months after the last dose of study treatment in such a manner that the risk of pregnancy is minimised. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to first treatment administration

13. Fertile men must be using adequate contraceptive measures throughout the study period and for up to 3 months after the last dose of study treatment if their partners are women of childbearing potential

14. The patient must have access to social insurance if applicable in the local regulations

15. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, those conditions should be assessed with the patient before registration in the trial

Exclusion criteria

If any of the following apply, the patient must not enter the study:

1. Nasopharyngeal carcinoma

2. History of brain or leptomeningeal involvement

3. History of other cancers except other synchronous head and neck squamous cell carcinomas, adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma of the skin or other cancer curatively treated with surgery and/or radiotherapy (with or without other anti-cancer therapy) and with no evidence of disease for at least 3 years

4. Albumin level < 35 g/L

5. Patients with weight loss ≥ 5% within the last 3 months

6. Recurrent pulmonary or upper airways infections (3 times or more in the last 3 months) requiring antibiotics and/or any infection requiring antibiotics within the last month before study entry

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NAME OF ACTIVE SUBSTANCE(S):	VINFLUNINE DITARTRATE

Exclusion criteria

7. Grade ≥ 2 peripheral neuropathy at study entry according to NCI-CTC AE (version 3.0)
8. Serum potassium < the lower limit of normal
9. ECG demonstrating a QT/QTc interval > 480 msec
10. A female is not eligible to enter the study if :
    . Pregnant or lactating
    . With positive pregnancy test at inclusion
11. Female of childbearing potential who is unwilling or unable to use a medically accepted method to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and at least 3 months following the last dose of study treatment
Male unwilling or unable to use a medically accepted method to avoid pregnancy throughout the study period and at least 3 months following the last dose of study treatment if their partners are women of childbearing potential.
12. Patients with any underlying medical condition that might be aggravated by treatment or which cannot be controlled *i.e.* active serious infection, poorly controlled diabetes mellitus, concurrent heart failure [New York Heart Association (NYHA) class III-IV] or with progressive or unstable angina, myocardial infarction within 6 months, and/or poorly controlled hypertension.
13. "Third space" fluids (pleural effusion, ascites, massive edema)
14. Concomitant treatment with any other anti-cancer therapy and contraindicated medication (see Section 6.1
15. Prior treatment with vinca-alkaloids and methotrexate
16. Participation into a clinical study of an investigational agent within 30 days before study entry

Test product, dose and mode of administration:

Patients randomised in the test arm (arm A) will receive IV vinflunine infused over 20 minutes at 280 mg/m² on day 1 and methotrexate administered as a bolus intravenous injection at 30 mg/m² on days 1 and 8 of each three-week cycle.

Administration of vinflunine requires prophylactic measures as follows:
- anti-emetic prophylaxis by giving a single dose of dexamethasone 8 mg or an equivalent dose of methylprednisolone just before the infusion
- prophylaxis of constipation combining dietary measures and the administration of laxatives from day 1 to day 5 of each cycle

Reference therapy, dose and mode of administration:

Patients randomised in the control arm (arm B) will receive methotrexate alone administered weekly as a bolus intravenous injection at the dose of 40 mg/m²/week.
One cycle of methotrexate is defined as a three-week period, *i.e.* 3 weekly administrations of methotrexate (days 1, 8 and 15).

Duration of treatment:

Patients will receive at least 2 cycles of study drug unless disease progression or unacceptable toxicity. After 6 weeks of study treatment, tumour response will be assessed: patients who respond or have stable disease will receive 2 additional cycles and will be reevaluated for tumour response. Patients with progressive disease will be removed while patients who respond or have stable disease will continue study treatment until disease progression.

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NAME OF FINISHED PRODUCT:	**JAVLOR®**
NAME OF ACTIVE SUBSTANCE(S):	VINFLUNINE DITARTRATE

Criteria for evaluation:

- Efficacy assessment:

The primary efficacy endpoint will be the overall survival defined as time from randomisation to death or last follow-up.

Secondary endpoints include the response and disease control rate by using RECIST (version 1.1), the response and disease control duration and the progression-free survival.

- Safety assessment will be assessed by:

. physical examination
. regular reporting of adverse event by using NCI CTC AE (version 3.0)

ECG to be performed on day 1 of cycle 1 before and after drug administration in both arms. Thereafter, ECG will be performed before drug administration every 2 cycles in both arms. After review of safety data including ECG results by the IDMC, the need for repeated ECGs before each cycle can be revised.
. complete blood cell counts performed on days 1 and 8 of each cycle in arm A and before each weekly administration in arm B
. serum biochemistry including AST, ALT, alkaline phosphatase, total bilirubin, urea, creatinine, calculated creatinine clearance, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate, total protein and albumin. Tests will be performed every 3 weeks, except glucose, total protein and albumin which will be performed every 6 weeks in both arms.

- Patient-reported outcomes will be assessed by using the QLQ-core 30 EORTC questionnaire and the QLQ-Head and Neck 35 EORTC module.

Statistical methods:

The primary objective of the study is to show that the combination of IV vinflunine and methotrexate is superior to methorexate alone in terms of overall survival. Patients will be randomised in a 1:1 ratio. The final analysis will require at least 437 deaths to detect a statistically significant difference in the median OS of 7.5 months in the test arm versus 5.5 months in the control arm. This number of events gives a 90% power to show a difference between the two treatment arms using a two-sided log-rank test at an alpha = 0.05 significance level.

An expected total number of 530 patients randomised were planned. An approximately 19 months accrual period was planned.
Following the decision to stop the recruitment:
- The statistical analysis will actually be conducted on the 459 randomised patients.
- 325 events are expected to observe at the end of study allowing a power of 80%.

Whatever the number of events at the end of study, the final analysis of OS (primary analysis) will be performed on the ITT population.
Only descriptive analyses will be performed on all secondary efficacy analyses for ITT population.

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NAME OF ACTIVE SUBSTANCE(S):	VINFLUNINE DITARTRATE

Statistical methods (ctd):

The primary efficacy analysis will be led on the Overall Survival. The hypothesis of superiority will be accepted if the p-value from a stratified log-rank test is smaller than 0.05. The stratification factors will be those used at the time of randomisation except center because of the high number of participating centers in the study:

- WHO performance status (0 versus 1),
- Refractory or resistant to platinum versus other,
- Prior radiotherapy (yes versus no),
- Prior treatment with any anti-EGFR medication (yes versus no).

The primary efficacy population will be the Intent-to-Treat Population (ITT). As a supportive analysis, Overall Survival will be also analysed on the Eligible population.

The Progression-Free Survival (PFS) will be performed on the ITT and eligible populations. A stratified log-rank test will be used in order to compare the two treatment arms with the same stratification factors defined above.

The Objective response Rate (ORR) and Disease control Rate (DCR) will be compared with a Cochran-Mantel-Haenszel (CMH) test between the two treatment arms. Furthermore, the ORR and DCR will be estimated and compared between the two treatment arms in the subgroups of patients entering the study with measurable disease. These analyses will be performed on the ITT and evaluable for response populations.

The duration of response and disease control will be also analysed on the ITT and evaluable for response populations. A stratified log-rank test will be used in order to compare the two treatment arms with the same stratification factors defined above.

Multivariate analyses of Overall Survival, PFS, ORR and DCR will be performed to take account of pronostic factors. A stratified Cox proportional hazards and a logistic regression will be used.

The safety analysis will be performed in the evaluable population for safety. Haematological parameters, febrile neutropenia, biochemical parameters and non haematological toxicities will be assessed. For haematological and biochemical parameters, the worst NCI CTCAE version 3.0 grade will be presented by patient and by cycle. For non haematological toxicities, the worst NCI CTCAE version 3.0 grade will be presented by patient.

Health-related quality of life will be assessed using the QLQ-core EORTC questionnaire and the QLQ-Head and Neck module.

There will be one early safety review after 40 are randomised (20 in each arm) and treated for at least 1 cycle.
An interim analysis based on the non progression rate at 6 weeks will be performed after tumour response data from the first 100 randomised patients in the test arm become available. The main purpose of this interim analysis is to stop the study if result indicating poor efficacy of the test regimen is observed. It is assumed that the test arm will be of no further interest in the second-line treatment of SCCHN patients if the observed non-progression rate at 6 weeks (first tumour assessment scheduled) is less than the lower limit of the 95% CI of the expected non-progression rate at 6 weeks.
Assuming that this expected non-progression rate at 6 weeks is equal to 61%, the 95% CI is [51%-71%] and the study will be stopped prematurely if $\geq$ 49 progressions (or deaths for progression) out of 100 evaluable patients for efficacy will be observed.

Safety and efficacy results of the interim analyses will be reviewed by an IDMC.

End of study

The end of study is the date of the last patient study treatment administration plus 30 days.

No follow-up visit will be performed. At the time of the amendment PA11:
- Patients under treatment will stop the study at the EOT.
- Patients under follow-up will stop immediately.

Table 1: Study flow chart

Required assessments	Screening period	Treatment period		End of treatment (f)	Follow-up (g)
Timing	**Day - 21 to - 1**	**Day 1 every cycle**	**Every 6 weeks**		
Signed informed consent	X (a)				
Demographic data					
Demography/Medical History/Diagnosis	X				
Serum or urine pregnancy test in women of childbearing potential	X (j)				
Physical Examination/Vital signs/Weight	X (b)	X		X	
WHO Performance Status	X (b)	X		X	X
Safety					
Electrocardiogram (ECG)	X (m)	X (m)			
Pre-treatment events/Adverse events/SAE	X (k)	X		X	X
Complete blood cell count (l)	X (b)	X (c) (within 24 hours)		X	
Blood chemistry (d)	X (b) (e)	X	X (e)	X (e)	
Concomitant medications/Blood Products	X(k)	X		X	
Efficacy (i)					
Cervical CT-Scan or MRI	X		X	X	X (h)
Chest/upper abdominal CT-Scan or MRI	X		X	X	X (h)
Other imaging if necessary	X		X	X	X (h)
Health-related quality of life					
EORTC QLQ-C30 and QLQ-H & N 35	Before randomisation within 24h		X	X	

(a) Prior to any study procedure.
(b) Within 7 days prior to first study drug treatment.
(c) CBCC performed on days 1 and 8 in arm A; on days 1, 8 and 15 in arm B
(d) Transaminases, alkaline phosphatase, total bilirubin, urea, creatinine, calculated (Cockroft-Gault) creatinine clearance , calcium, sodium, potassium, magnesium, chloride, bicarbonate.
(e) Glucose, total protein and albumin to be performed in addition.
(f) Within 30 days after study treatment discontinuation.
(g) Until disease progression: every 6 weeks. After disease progression, every month for the first 6 months and then every 3 months until death.
At the time of the amendment PA11, no more follow-up visit will be performed.
(h) In case of treatment discontinuation for other reason than PD, all efficacy assessments must be performed every 6 weeks from time of randomisation until disease progression is documented, then survival information will be collected approximately every month for the first 6 months then every 3 months until death.
At the time of the amendment PA11, these assessments will not be performed.
(i) Tumour assessment is to be performed every 6 weeks (+/- 3 working days) from randomisation (regardless of the timing of treatment cycles) : all lesions found at baseline should be re-investigated at each tumour assessment. Additional examinations may be performed if appearance of new lesions is suspected.
(j) Within 72 hours prior to first study drug treatment
(k) Within 2 weeks prior to first study drug treatment.
(l) To be repeated in the event of fever or infection according to institutional standards and investigator decision.
(m) To be performed within 7 days before randomisation and repeated on D1 of the first cycle before and after drug administration in both arms. Thereafter, to be repeated before drug administration every two cycles in both arms. After review of safety data including ECG results by the IDMC, the need for repeated ECGs before each cycle can be revised

APPROVAL FORM

STUDY: L00070 IN 309 F0

PROTOCOL Version No. 7 dated: 5th February 2016

Sponsor's representatives

Head of Development Platform

Name : François BRACKMAN Date : Signature :

Study Chairman

Jan VERMORKEN Date : Signature :
Department of Medical Oncology
University hospital Antwerp
Edegem, Belgium

COUNTRY COORDINATING INVESTIGATOR SIGNATURE FORM*

STUDY: L00070 IN 309 F0

PROTOCOL Version No. 7 dated: 5th February 2016

Country Coordinating Investigator:**

Name Date: Signature:

* *if required by local regulation*
** *if applicable or principal investigator for a national study*

INVESTIGATOR SIGNATURE FORM

STUDY: L00070 IN 309 F0

PROTOCOL Version No. 7 dated: 5th February 2016

By my signature below, I, Dr. _____ hereby confirm that I agree:

- to conduct the trial described in the protocol n° L00070 IN 309 F0 Version No. 7 dated 5th February 2016 in compliance with GCP, with applicable regulatory requirements and with the protocol agreed upon by the sponsor and given approval/favourable opinion by the Ethics Committee ;
- to document the delegation of significant study related duties and to notify the sponsor of changes in site personnel involved in the study ;
- to comply with procedures for data recording and reporting ;
- to permit monitoring, auditing and inspection ;
- to retain the trial-related essential documents until the sponsor informs these documents are no longer needed.

Furthermore, I hereby confirm that I will have and will use the availability of adequate resources, personnel and facilities for the conduct of this trial.

Date: Signature:

Sponsor's personnel

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TABLE OF CONTENTS

CONTENTS OF TABLES

APPENDICES

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine amino Transferase
ANC	Absolute Neutrophil Count
AST	Aspartate amino Transferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
BSA	Body Surface Area
BSC	Best Supportive Care
CA	Competent Authorities
CBCC	Complete Blood Cell Count
CI	Confidence Interval
CMV	Cisplatin-Methotrexate-Vinblastine
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRF	Case Report Form
CRT	Chemoradiation
CSC	Clinical Study Coordinator
CT	Chemotherapy
CT scan	Computed Tomography Scan
CVL	Central Venous Line
D	Day
DCR	Disease Control Rate
DL	Dose Level
DLT	Dose Limiting Toxicity
DVFL	4-O-DeacetylVinflunine
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	Epidermic Growth Factor Receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End Of Treatment
FDA	Food and Drug Administration
5-FU	5 Fluorouracil
GCP	Good Clinical Practice
Hb	Haemoglobin
HR	Heart Rate
ICH	International Conference on Harmonisation
ICT	Induction Chemotherapy
IDMC	Independent Data Monitoring Committee
i.p.	Intraperitoneal
IRPF	Institut de Recherche Pierre Fabre
IRRC	Independent Response Review Committee
ITT	Intent To Treat
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
KPS	Karnofsky Performance Status
LD	Longest Diameter

MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximal Tolerated Dose
M-VAC	Methotrexate-Vinblastine-Doxorubicin-Cisplatin
N	Number
NC	No Change
NCI CTC AE	National Cancer Institute - Common Toxicity Criteria for Adverse Events
NS	Normal Saline
NSCLC	Non Small Cell Lung Cancer
ORR	Objective Response Rate
OR	Overall response
PD	Progressive Disease
PFM	Pierre Fabre Médicament
PFS	Progression-Free Survival
PLT	Platelets
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PS	Performance Status
pt (s)	Patient (s)
RD	Recommended Dose
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous-Cell Carcinoma of the Head and Neck
s.d.	Standard Deviation
SD	Stable disease
SGOT (AST)	Serum Glutamic Oxalo-Acetic Transaminase
SGPT (ALT)	Serum Glutamic Pyruvic Transaminase
TCCU	Transitional Cell Carcinoma of the Urothelial tract
T_{max}	Time to reach the C_{max}
TTP	Time To Progression
ULN	Upper Limit of Normal
VFL	Vinflunine
WBC	White Blood Cell(s)
WHO	World Health Organization
WNL	Within Normal Limits

1. INTRODUCTION

1.1. BACKGROUND ON THE STUDY

1.1.1. Background on the disease

Squamous cell carcinoma of the head and neck (SCCHN) represents 5% of newly diagnosed cancers in adult patients. Worldwide more than 500.000 new cases are projected annually and approximately 300 000 deaths are attributed to this disease.

It is a potentially curable malignancy when diagnosed at an early stage. Unfortunately, patients often present with an advanced locoregional disease. Despite aggressive local management, fewer than 30% of those patients are cured. The majority will die of locoregional recurrences. Approximately, 10% of newly diagnosed patients and up to 30% of relapsed patients will present with distant metastases. Locoregional recurrence not suitable for local therapy and metastatic disease are incurable and have been managed palliatively with chemotherapy.

Many single agents have been shown to produce tumour response including methotrexate, cisplatin, carboplatin, bleomycin, doxorubicin, taxanes, vinblastin, vinorelbine and 5-fluorouracil (5-FU) (Colevas D., 2006). Combination regimens produced statistically higher response rates than single agents (Forastiere A., 1992 ; Jacobs C., 1992). The combination of cisplatin and 5-FU emerged as a favoured treatment in the 1980s and 1990s. This was based on the higher response rates reported in recurrent/metastatic disease (Jacobs C., 1992 ; Clavel M., 1994) but at the expense of greater toxicity and without demonstrating improved survival. Triple-agent regimen, usually docetaxel, cisplatin and 5FU, was shown to be superior to cisplatin plus 5 FU but increased toxicity limits its use to induction chemotherapy (Posner M, 2007, Vermorken JB, 2007c). Cetuximab demonstrated significantly prolonged locoregional control and overall survival when used in combination with radiotherapy in locally advanced SCCHN (Bonner J.A., 2006). More recently, the addition of cetuximab to platinum-based chemotherapy improved overall survival when given as first-line treatment in patients with recurrent/metastatic SCCHN (Vermorken JB, 2008). The median overall survival was increased from 7.4 months to 10.1 months by the addition of cetuximab. However,

approximately one third of patients respond to first-line platinum-based therapy. Thus, there is clearly an unmet therapeutic need for the treatment of recurrent/metastatic SCCHN who failed platinum-based therapy.

For patients with incurable recurrent/metastatic SCCHN who failed platinum-based therapy, single agent methotrexate remains a standard option (Pivot X., 2001 ; Stewart S., 2009). In this setting, the standard regimen of methotrexate is 40 to 60 mg/m² intravenously weekly (Colevas D., 2006). Methotrexate is eliminated primarily in the urine whereas hepatic metabolism pathway is limited. After intravenous administration, about 60-80% of the dose is excreted in urine as unchanged drug within 24 hours post-dosing and biliary elimination remains low (Seideman P., 1993). The expected adverse effects of methotrexate are mucositis and myelosuppression, other side effects include vomiting, diarrhoea, transient erythematous skin rash and transient elevations of liver enzymes. Response rates ranging from 3.9% to 10.8% and median overall survival between 3.7 and 6.7 months were reported. Differences in efficacy results can be explained by different selection criteria and improvement in the management of SCCHN between 1992 and 2010. Efficacy results published on the use of methotrexate single agent are shown below.

Table 2: Efficacy of methotrexate single agent in SCCHN

Author (years)	Disease setting	N of patients	Response rate (%)	Disease control rate (%)	Progression-free survival (months) [95% CI]	Overall survival (months) [95% CI]
Forastiere A., 1992	First-line	88	10	60	NA	5.6 [NA]
Schornagel J.H., 1995	First-line	133	16	47	NA	6.0 [NA]
Vermorken JB, 1999	First-line	42	19.5	-	2.0 [1.6-3.7]	6.1 [5.5 - 8.7]
Pivot X., 2001	Failure after induction CT or chemoradiotherapy / Second-line	46	10.8	41.3	1.5 [1-18]	3.7 [0.5-18.0]
Stewart S., 2009	Second-line or unsuitable for platinum-based CT	161	3.9	48.0	NA	6.7 [NA]
Machiels JP, 2011	Failure of at least one platinum-based CT	95*	1.1	27.0	2.0 [2-2.4]	5.2 [4.1 - 6.4]

* patients randomised to BSC : 78% of them received methotrexate
NA : Not Available

Among new agents which were tested in recurrent / metastatic SCCHN patients who failed platinum-based therapies, anti-EGFR antibodies have been the most promising (Goerner M., 2010). In a retrospective analysis, J. Vermorken (Vermorken JB, 2007a) reported the potential of cetuximab to prolong survival. Cetuximab used alone (Vermorken JB, 2007b) or in combination

with cisplatin (Herbst R., 2005) or carboplatin (Baselga J., 2005) achieved response rates from 10% to 13%, disease control rates of 46% to 56% and overall survival between 5.2 months and 6.1 months. However zalutumumab failed to demonstrate a significant increase in overall survival over best supportive care (78% of patients received methotrexate) despite slight improvement in median progression-free survival from 8.4 to 9.9 weeks (Machiels JP, 2011). Cetuximab has now been granted marketing authorization approval in combination with radiotherapy for locally advanced disease and in combination with platinum-based chemotherapy for recurrent / metastatic disease by the EMA and the FDA.

With the use of cetuximab in earlier stages of SCCHN, new effective therapeutic options are urgently needed in patients with incurable recurrent / metastatic disease who failed platinum-based chemotherapy. Methotrexate remains an option but its activity is poor as shown in Table 2.

1.2. BACKGROUND ON IV VINFLUNINE

1.2.1. Chemistry and pharmacology

Vinflunine (VFL) is a novel microtubule inhibitor obtained by semi-synthesis using an original chemical approach in order to selectively modify the catharanthine moiety of the *Vinca* alkaloid scaffold (Fahy J, 1997).

Research was focused on identifying an original chemical approach that induced dramatic changes in the skeleton of the molecule and optimise the therapeutic index of these derivatives. This investigation has focused on the reactivity of these functionalised compounds in superacidic media. A semi-synthetic microtubule-targeting agent, vinflunine, was selected on the basis of its high level of *in vivo* antitumour activity against experimental tumours compared with other agents of the same class. The optimal structural modification of this compound is the introduction of 2 fluorine atoms at the 20' position, a part of the molecule previously inaccessible by classic chemistry (Jacquesy JC, 2000). Pharmacological investigations have highlighted the essential contribution of the fluorine atoms to this antitumour activity (Duflos A, 2002).

Classic primary pharmacological screening of a large series of derivatives centred on *in vitro* cytotoxicity tests and *in vivo* activity assays; vinflunine was selected for detailed preclinical

investigations essentially on the basis of its high *in vivo* antitumour activity compared with other compounds of the same class.

Vinflunine antitumour activity was fully demonstrated against a large and varied panel of murine and xenograft models. It was proved to be active against 5 of the 7 murine 'solid' tumours tested and against 13 human tumour xenografts yielding a response rate of 45%, with marked tumour growth inhibition and/or tumour regressions (Hill BT, 1999). This figure meets the current NCI criteria for a new agent, predicted to have some degree of clinical activity (Johnson JI, 2001). Furthermore, superiority of vinflunine relative to vinorelbine (VRL) was clearly established. Among ten experimental human tumour models, VFL proved active in 6 tumours (including 2 with a high activity rating) whilst vinorelbine was active against 4 tumours (including only 1 high activity rating). This activity was usually achieved in the absence of any significant body weight loss (i.e. < 15%) or early deaths, in tumour-bearing animals. The high level of tolerance to VFL and its durable antitumour activity provided a favourable profile for further development of this new product. (Kruczynski A, 1998b ; Hill BT, 2001).

Vinflunine interacts with tubulin at the vinca-binding domain and inhibits tubulin assembly by perturbing microtubule dynamics and mitotic spindles without affecting assembled microtubules. VFL exhibits the weakest overall affinity for tubulin and the most readily reversible interaction with tubulin (Kruczynkski A, 1998a ; Kruczynski A, 2001). This characteristic was not considered as deleterious for the drug since it has been shown that the strength of the binding of vinca-alkaloids was not necessarily related to antitumour efficacy (Singer WD, 1989). These data were consistent with the hypothesis that VFL was likely to result in reduced neurotoxicity relative to vincristine, vinblastine and VRL (Lobert S, 1998) and in vitro safety pharmacology data confirmed this hypothesis. This potential for lower neurotoxicity represents another important difference compared with classic vinca-alkaloids or other microtubule inhibitors like taxanes or new epothilones like ixabepilone.

Data on the resistance profile of the compound added weight to its potential value as a candidate for clinical development. VFL, like the other vinca-alkaloids, participates in Pgp-mediated MDR, with tumour cells selected for VFL resistance over-expressing Pgp, yet MDR tumour cell lines proved generally less cross resistant to VFL relative to the other vinca-alkaloids (Etievant C, 1998).

More importantly, VFL induces drug resistance far less readily than vinorelbine in terms of the number of passages required selecting for total resistance and the level of resistance ultimately obtained. In vitro full resistance was reached in 8 months versus 2 months after 2-fold IC50 exposures to VFL and VRL respectively. In another model, *in vivo* complete resistance to VFL was obtained after 36 weeks exposure at sub-therapeutic doses compared to only 11 weeks for VRL (Etievant C, 2001).

1.2.1.1. Dose and pharmacokinetics

Following i.v. administration to patients, vinflunine is eliminated according to a multi-exponential decay with a rapid decrease of blood concentrations during the first hour. The terminal half-life is approximately 40 hours. The volume of distribution is large, 1,100 to 4,400 litres (about 19 to 59 L/kg) suggesting important tissue distribution and uptake. Total clearance in blood is large (43.9 L/h, 0.60 L/h/kg). Vinflunine binding to blood cells is moderate, and that to platelets is negligible. The binding of VFL to human serum proteins is moderate; there was no binding to α1-glycoprotein. Several metabolites are observed in blood, the main one being DVFL, which is also active. The terminal half-life of DVFL (approximately 5 days) is longer than that of unchanged compound. Excretion of VFL and its metabolites is higher in faeces than in urine (2/3 and 1/3 of the recovered radioactivity, respectively (IRPF CSR 103, Focan C, 2002, Bennouna J, 2003, Bennouna J, 2008).

VFL pharmacokinetics (PK) are not affected by liver dysfunction (Paule B, 2007). The VFL clearance is reduced in patients with low serum creatinine clearance (20 to 60 ml/min) (Vinflunine Investigator Brochure n° 16.1). Similarly, a phase I study in elderly patients demonstrated that VFL clearance was decreased in the oldest patients (80 years and beyond) whereas it was unchanged in patients between 70 and < 80 years compared to younger ones (< 70 years) (Tourani JM, 2010). Strong CYP3A4 inhibitors have been shown to inhibit the VFL metabolism as CYP 3A4 is the only isoform of cytochrome P450 involved in the oxidative metabolism of vinflunine.

Vinflunine clinical development started in December 1998. Three Phase I trials were conducted in order to determine the maximum tolerated dose (MTD) and the recommended dose according to

three different schedules of vinflunine administration: on day 1 every 3 weeks, weekly administration, on day 1 and day 8 every 3 weeks (Bennouna J, 2003; Delord JP, 2001, Puozzo C, 2001, Vermorken JB, 2003; Johnson P, 2006).

Based on safety, pharmacokinetic and antitumour activity data from these three phase I trials, vinflunine every 3 weeks schedule was considered optimal. Following a preliminary safety survey performed on the first 28 patients treated in the early phase II studies, a dose adjustment to vinflunine 320 mg/m² was used over a 20 minutes infusion for all subsequent patients included in clinical trials (Vinflunine Investigator Brochure n° 16.1).

1.2.1.2. Overview on clinical development

An international program of phase II studies with vinflunine as a single agent has been carried out in chemonaive patients, and also as salvage therapy in order to determine the tumour response in a large spectrum of solid tumours: melanoma, renal carcinoma, ovarian cancer (after 1st line paclitaxel/platinum), mesothelioma (1st line), colon carcinoma (after oxaliplatin/irinotecan-containing regimens), non-small cell lung cancer (2nd line after platinum-containing regimen), in transitional cell carcinoma of the urothelium (2nd line after platinum-containing regimen) and breast carcinoma (after anthracyclines/taxane exposure).

Phase III studies were completed in advanced transitional cell carcinoma of the urothelial tract (TCCU) and in advanced non-small cell lung cancer (NSCLC). In both trials VFL was given as second-line after failure of prior platinum-based chemotherapy. In advanced TCCU, VFL demonstrates a survival advantage over best supportive care (Bellmunt J., 2009) and was granted a marketing authorization approval in this indication by the EMA. In advanced NSCLC, VLF showed similar efficacy results to docetaxel (Krzakowski M., 2010).

Three phase III studies are carried out in advanced breast cancer (Vinflunine Investigator Brochure n° 16.1).

1.2.1.3. Safety profile of vinflunine as a single agent

Safety data from 1076 patients treated at the initial dose of 320 mg/m² and 483 patients treated at the initial dose of 280 mg/m² were collected and analysed in the clinical studies sponsored by PFM. The table below gives the incidences of drug-related adverse events reported in at least 5% of patients. Detailed information is provided in the Investigator Brochure no. 16.1 (November 2013).

Table 3: Haematological results and drug-related adverse events (> 5%) per patient according to MedDRA by worst grade (NCI CT version 3.0)

System Organ Class / Preferred term	VFL 320 mg/m² (n = 1076)				VFL 280 mg/m² (n = 483)			
	Any grade		Grade 3 - 4		Any grade		Grade 3 - 4	
	N	%	N	%	N	%	N	%
Haematological Laboratory Test Results	**Haematological Laboratory Test Results (1064 pts : 12 not evaluable)**				**Haematological Laboratory Test Results (476 pts : 7 not evaluable)**			
Anemia	898	84.4	80	7.5	398	83.6	35	7.4
Leucopenia	754	70.9	326	30.6	206	43.3	58	12.2
Neutropenia	742	69.7	487	45.8	187	39.3	59	12.4
Thrombocytopenia	361	33.9	29	2.7	107	22.5	11	2.3
Febrile neutropenia	53	5.0	53	5.0	15	3.1	15	3.2
Gastrointestinal disorders								
Abdominal pain	265	24.6	54	5.0	100	20.7	23	4.8
Abdominal pain upper	64	5.9	5	0.5	16	3.3	0	0
Constipation	567	52.7	121	11.2	210	43.5	44	9.1
Diarrhoea	124	11.5	9	0.8	44	9.1	9	1.0
Nausea	446	40.3	28	2.6	150	31.1	15	3.4
Stomatitis	326	29.4	22	2.0	98	20.3	5	1.0
Vomiting	310	28.0	29	2.7	93	19.3	13	2.7
General disorders and administration site conditions								
Chest pain	55	5.1	14	1.3	14	1.3	1	0.2
Fatigue	583	54.2	133	12.4	107	22.2	34	7.0
Injection site reaction	190	17.7	4	0.4	71	14.7	0	0
Pyrexia	98	9.1	3	0.3	33	6.8	2	0.4
Investigations								
Weight decreased	211	19.6	3	0.3	66	13.7	2	0.4
Metabolism and nutrition disorders								
Decreased Appetite	281	26.1	23	2.1	101	20.9	11	2.3
Musculoskeletal and connective tissue disorders								
Arthralgia	83	7.7	11	1.0	37	7.7	2	0.4
Myalgia	208	19.3	38	3.5	61	12.6	6	1.2
Pain in jaw	78	7.2	7	0.7	19	3.9	0	0
Nervous system disorders								
Headache	90	8.4	6	0.6	15	3.1	1	0.2
Paraesthesia	89	8.3	4	0.4	14	2.9	1	0.2
Peripheral sensory neuropathy	65	6.0	2	0.2	28	5.8	3	0.6
Skin and subcutaneous tissue disorders								
Alopecia	31	2.9	NA	NA	72	14.9	NA	NA

The majority of patients treated at the initial dose of 280 mg/m² were TCCU patients who presented with WHO performance status of 1 and/or underwent prior pelvic irradiation. As a consequence, the safety profiles observed in patients treated at 320 mg/m² and in those treated at 280 mg/m² are similar. This finding justifies starting VFL at the lower dose of 280 mg/m² in patients with decreased PS.

The main adverse events were neutropenia with grade 3-4 neutropenia in 45.8% of patients at 320 mg/m² and 12.4% at 280 mg/m² and constipation reported in 52.7% of patients at 320 mg/m² and 43.5% of these at 280 mg/m². It is noteworthy that no systematic prophylaxis with laxatives was recommended at this stage of VFL clinical development.

Clinical data demonstrated a moderate, frequent but reversible neurotoxicity (peripheral neuropathy, headache, dizziness, neuralgia).

1.2.1.4. Vinflunine and methotrexate in combination

A phase I study has been designed to determine the recommended dose of the combination of VFL plus methotrexate in patients with recurrent or metastatic SCCHN previously treated with a platinum-based chemotherapy and also to assess the safety, the pharmacokinetics profile and the antitumour activity of the combination. Preliminary clinical results are available (Preliminary Clinical Evaluation).

VFL was given at a fixed dose of 280 mg/m² on day 1 in combination with methotrexate 20, 30 or 40 mg/m² administered on days 1 and 8 of every three-week cycle.

Cohorts of a minimum of 3 to 6 evaluable patients per dose level were intended to be enrolled.

The criteria of MTD were met at the first DL (VFL 280 mg/m² + MTX 30 mg/m²) due to the occurrence of one DLT in 2 out of 3 evaluable patients treated at this DL (one grade 3 constipation and one grade 3 febrile neutropenia). The DL -1 (VFL 280 mg/m² + MTX 20 mg/m²) was thus investigated and determined to be the RD and thus tested in 10 patients: DLT was observed in 2 out of 10 evaluable patients treated at this DL (one grade 3 neutropenic infection and one grade 3 ileus).

The study protocol was then amended to restrict the population to fit patients (serum albumin ≥ 35g/L; weight loss < 5% within the last 3 months and absence of recurrent, i.e. ≥ 3 times pulmonary or upper airway infections, requiring antibiotics in the last 3 months). In this population of fit patients, two DLs were tested: VFL 280 mg/m² + MTX 30 mg/m² (DL1bis) and VFL 280 mg/m² + MTX 40 mg/m² (DL2bis). At DL1bis, 3 evaluable patients, among 4 treated patients, were treated without any dose limiting toxicity (DLT). The higher DL2bis was then investigated and identified as the MTD due to the occurrence of DLT in 2 out of 6 patients (one grade 3 and one grade 4 febrile neutropenia). The RD was VFL 280 mg/m² on D1 + MTX 30 mg/m² on D1 and D8, every 3 weeks.

At the RD, determined in fit patients, having received 1 to 3 cycles, the main haematological toxicity was neutropenia: grade 3 neutropenia in 1 patient and grade 4 neutropenia in 3 patients. Only one grade 4 non-haematological toxicity was observed in one patient (asthenia) and the most common grade 1-2 non-haematological toxicities included constipation, fatigue, abdominal pain, nausea, and alopecia.

A total of 31 patients were enrolled in the study (pre- and post-amendment), 20 of whom having been considered evaluable for response.

Clinical activity was shown as evidenced by 3 responses: one confirmed complete response and 2 confirmed partial responses reported in the 20 patients evaluable for response (15%) and additional stable disease in 8 patients (40 %). Therefore, disease control was achieved in 11 patients (55%).

Vinflunine pharmacokinetics were investigated on day 1 of cycle 1 when VFL was combined with methotrexate (MTX) and on day 1 of cycle 2 when VFL was administered alone and MTX given two days later. Methotrexate pharmacokinetics was also assessed on day 1 of cycle 1 when both drugs were combined and on day 8 of cycle 1 when MTX was administered alone.
Preliminary PK analysis showed no obvious mutual drug-drug interaction between vinflunine and methotrexate.

1.3. STUDY RATIONALE

For patients relapsing after platinum-based therapy, few data are available. Nolatrexed, a new synthase inhibitor demonstrated a similar activity to methotrexate in this setting (Pivot X., 2001). Cetuximab, a monoclonal antibody designed to block human EGFR, was investigated in recurrent/metastatic SCCHN patients refractory to cisplatin-based chemotherapy. In this setting, the combination of cetuximab and cisplatin achieved response rates of 10% with median overall survival of 5.2 and 6.1 months in 2 phase II studies (Baselga J., 2005 ; Herbst R., 2005). As a single agent, cetuximab showed a 13% response rate with median overall survival of 5.9 months in another phase II study carried out in the same population (Vermorken JB, 2007b). The current use of cetuximab associated with radiotherapy in localized disease and associated with platinum-based chemotherapy in the first-line setting stresses the need for new therapeutic options at later stages of SCCHN.

Vinca-alkaloids demontrated activity in SCCHN (Colevas D., 2006). Single agent vinorelbine showed activity after first-line cisplatin-based chemotherapy (Testolin A., 1994 ; Porta C., 2001). Vinflunine demonstrated superior antitumour activity to vinorelbine in preclinical animal models. This translates into a well-established efficacy of vinflunine in the second-line treatment of TCCU and NSCLC after platinum failure.

Vinca-alkaloids have been successfully combined with methotrexate in a variety of solid tumours. In the first-line treatment of advanced TCCU, M-VAC is still considered the most effective regimen despite its toxicity (Calabro F., 2007) ; CMV is generally considered similar in efficacy although no direct comparison has been made (Harker W.G., 1985). In metastatic breast cancer, the combination of vinorelbine, methotrexate and 5-FU used as first-line therapy produced a 50% response rate (Elomaa J., 2003). Methotrexate plus vinblastine with or without platinum achieved a 53% response rate and median overall survival of 14 months in malignant mesothelioma (Hunt K., 1996). In SCCHN relapsing after cisplatin plus 5-fluorouracil, a regimen combining vinorelbine, bleomycin and methotrexate showed activity with a response rate of 27% and acceptable toxicity (Iop A., 1998). Recent preliminary phase I results of the vinflunine plus methotrexate combination in SCCHN, based on a clinical review, show encouraging antitumour activity and an acceptable safety profile (Preliminary Clinical Evaluation).

Therefore the combination of vinflunine and methotrexate appears a promising salvage regimen after platinum failure.

The present study has been designed as a multicenter, randomised phase III study which will compare the combination of IV vinflunine with methotrexate to methotrexate alone in SCCHN patients having failed platinum-based therapy.

2. STUDY OBJECTIVES

- Primary objective: to compare the overall survival of IV vinflunine in combination with methotrexate versus methotrexate alone in incurable recurrent/metastatic SCCHN patients having failed platinum-based chemotherapy.

- Secondary objectives:
  - to evaluate the response and disease control rate in the 2 study arms.
  - to assess the response and disease control duration in the 2 study arms
  - to assess the progression-free survival in the 2 study arms.
  - to assess the safety profile in both arms
  - to compare the change in disease-related symptoms by using the EORTC quality of life questionnaire.

3. STUDY DESIGN

This is a multicenter, open-label, randomised phase III study of IV vinflunine in combination with methotrexate versus methotrexate alone in incurable recurrent/metastatic SCCHN patients having failed prior platinum-based chemotherapy.

Randomisation will be stratified according to a minimisation procedure (Pocock SJ, 1975) on the following baseline factors:

- WHO performance status (0 versus 1)
- Refractory or resistant to platinum versus other
- Prior radiotherapy (yes versus no)

- Prior treatment with any anti-EGFR medication (yes versus no)
- Center

Patients will be randomly assigned to receive in a 1 : 1 ratio one of the study arms :
- Arm A: IV vinflunine given at the dose of 280 mg/m² on day 1 and methotrexate administered at the dose of 30 mg/m² on days 1 and 8 of every three-week cycle.
- Arm B: methotrexate given at the dose of 40 mg/m²/week.

Overall survival will be the primary endpoint of the study. The final analysis will require at least 437 deaths. The study has been powered at 90 % to show an improvement of survival from 5.5 months in the control arm (Machiels JP, 2011) to 7.5 months in the test arm.

Throughout the study, patients will be closely monitored for safety evaluation and will be assessed for tumour response every 6 weeks (every 2 cycles). Patients will receive at least 2 cycles unless they experienced unacceptable toxicity or early disease progression. Patients who respond or have stable disease will receive 2 additional cycles and will be reevaluated for tumour response. Patients with progressive disease will be removed while patients who respond or have stable disease may continue study treatment until disease progression.

Tumour responses and date of progression will be evaluated for all randomised patients. After documentation of disease progression, patients were followed every month during the first 6 months and then every 3 months until death.

At the time of the amendment PA11, patients will be followed only 30 days after the last treatment administration.

An Independent Data Monitoring Committee (IDMC) which purpose is to protect the safety of trial participants, the credibility and validity of data, will be charged of reviewing the results of :

- an early safety review which will be conducted after 40 patients are randomised (20 in each arm) and treated for at least one cycle. The IDMC will review the safety data and make recommendations accordingly.
- an interim analysis which will take place when 100 randomised patients in the test arm have undergone the first tumour assessment scheduled 6 weeks from randomisation. This interim

analysis will evaluate the observed non-progression rate at 6 weeks and the safety in the test arm. Based on this interim analysis, the IDMC will determine whether the enrolment should continue or not. Because the projected accrual in the study can be slow, the patient enrolment will continue while waiting the decision of the IDMC.

Following this interim analysis, a futility analysis has been carried out.

The results of this analysis showed that the probability to demonstrate a significant benefit of overall survival at the time of the final analysis is very low.

As a consequence, the sponsor has decided to stop the recruitment of study patients on 16th October 2015.

4. STUDY POPULATION

4.1. INCLUSION CRITERIA

Patients must satisfy all the following inclusion criteria before they are allowed to participate in the study:

1. Patients must give written informed consent (personally signed and dated) before completing any study-related procedure

2. Histologically or cytologically confirmed recurrent and/or metastatic squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx or larynx

3. Documented progressive disease after chemotherapy for locoregionally advanced or recurrent / metastatic SCCHN which included a platinum derivative (cisplatin or carboplatin) that is not suitable for local therapy. Platinum-based chemotherapy can have been associated with cetuximab. Eligible patients include one of the following categories (see Appendix 9 for diagram):

- patients who have received induction chemotherapy (ICT) consisting of cisplatin plus 5-fluorouracil or docetaxel plus cisplatin plus 5-fluorouracil followed by radiotherapy alone or chemoradiation (CRT) or radiotherapy concomitant with cetuximab provided that recurrence occurs within 6 months of completing local therapy
- patients who have completed cisplatin-based CRT with or without ICT provided that

recurrence occurs within 6 months of completing local therapy. The minimum cumulative dose of cisplatin during CRT must be 200 mg/m².

- patients with recurrent and/or metastatic SCCHN who relapse after platinum-based (cisplatin or carboplatin) chemotherapy given in first-line with an interval < 12 months

- patients with metastatic SCCHN at diagnosis who have been treated with platinum-based (cisplatin or carboplatin) chemotherapy in first-line and relapse with an interval < 12 months.

The definition of failure is as follows:

- refractory disease: progression during platinum-based regimen

- resistant disease: progression during the time from completion of platinum-based chemotherapy but < 6 months after its completion

- or other type of failure: progression ≥ 6 months but < 12 months after completion of platinum-based chemotherapy

4. No more than one prior chemotherapy regimen for recurrent/metastatic disease. Prior treatments with targeted therapy used in monotherapy are allowed

5. Minimum interval of 4 weeks between the completion of first-line chemotherapy and randomisation

6. Measurable or non measurable disease

7. WHO performance status ≤ 1

8. Age ≥ 18 years and < 80 years

9. Adequate haematological function: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, haemoglobin ≥ 10g/dL.

10. Adequate hepatic function: transaminases ≤ 2.5 x Upper Limit of Normal (ULN), total bilirubin ≤ 1.5 x ULN, alkaline phosphatase ≤ 5 x ULN

11. Adequate renal function: calculated (Cockroft-Gault) creatinine clearance > 60 ml/min

12. Women of childbearing potential must be using a medically accepted method of contraception (barrier methods, oral contraceptives, intrauterine devices) to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and for up to 3 months after the last dose of study treatment in such a manner that the risk of pregnancy is minimised. Women of childbearing potential must have a negative serum or urine pregnancy test within 72 hours prior to first treatment administration

13. Fertile men must be using adequate contraceptive measures throughout the study period and for up to 3 months after the last dose of study treatment if their partner are women of childbearing potential

14. The patient must have access to social insurance if applicable in the local regulations

15. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, those conditions should be assessed with the patient before registration in the trial.

4.2. EXCLUSION CRITERIA

If any of the following apply, the patient must not enter into the study:

1. Nasopharyngeal carcinoma

2. History of brain or leptomeningeal involvement

3. History of other cancers except other synchronous head and neck squamous cell carcinomas, adequately treated in situ carcinoma of the cervix uteri, basal or squamous cell carcinoma of the skin or other cancer curatively treated with surgery and/or radiotherapy (with or without other anti-cancer therapy) and with no evidence of disease for at least 3 years

4. Albumin level < 35 g/L

5. Patients with weight loss ≥ 5% within the last 3 months

6. Recurrent pulmonary or upper airways infections (3 times or more in the last 3 months) requiring antibiotics and/or any infection requiring antibiotics within the last month before study entry

7. Grade $\geq$ 2 peripheral neuropathy at study entry according to NCI-CTC AE (version 3.0)

8. Serum potassium < the lower limit of normal

9. ECG demonstrating a QT/QTc interval > 480 msec

10. A female is not eligible to enter the study if :

. Pregnant or lactating

. With positive pregnancy test at inclusion

11. Female of childbearing potential who is unwilling or unable to use a medically accepted method to avoid pregnancy during the 2 months preceding the start of study treatment, throughout the study period and at least 3 months following the last dose of study treatment

Male unwilling or unable to use a medically accepted method to avoid pregnancy throughout the study period and at least 3 months following the last dose of study treatment if their partners are women of childbearing potential

12. Patients with any underlying medical condition that might be aggravated by treatment or which cannot be controlled i.e. active serious infection, poorly controlled diabetes mellitus, concurrent heart failure [New York Heart Association (NYHA) class III-IV] or with progressive or unstable angina, myocardial infarction within 6 months, and/or poorly controlled hypertension.

13. “Third space” fluids (pleural effusion, ascites, massive edema)

14. Concomitant treatment with any other anti-cancer therapy and contraindicated medication (see Section 6.1)

15. Prior treatment with vinca-alkaloids and methotrexate

16. Participation into a clinical study of an investigational agent within 30 days before study entry

4.3. NUMBER OF PATIENTS

An estimated sample size of 265 randomized patients in each arm was expected, i.e. a total of 530 randomised patients. The required number of events to observe at the final analysis is 437 deaths. An approximately 19 months accrual period was planned.

Following the decision to stop the recruitment, 459 patients have actually been enrolled in this study with a 1:1 ratio for randomization.

The details of the original sample size are given in Section 11.1.

5. STUDY TREATMENT

5.1. STUDY DRUG ADMINISTRATION

5.1.1. Vinflunine and methotrexate (arm A)

Descriptions of study drugs, storage, packaging, labelling and drug accountability are given in Section 10.

Patients randomised to arm A will receive vinflunine on day 1 as a 20 minute IV infusion at 280 mg/m² and methotrexate on days 1 and 8 as a bolus intravenous injection at 30 mg/m² of every three-week cycle.

The total dose to be given will be calculated according to body surface area (BSA). In calculating BSA, actual heights and weights should be used. BSA should be recalculated prior to the next cycle dosing.

5.1.1.1. Vinflunine

The calculated dose of vinflunine will be administered as follows:

1. Mix vinflunine in a 100 mL bag of normal saline (NS) or 5% glucose solution.
2. **Establish venous access on a large vein preferably in the upper part of the forearm or using a central venous line (CVL).**

The veins of the dorsum of the hand and veins close to joints should be avoided.

3. Start a venous infusion of 500 mL bag of NS or 5% glucose solution at a free-flowing rate to assess the patency of the vein.

4. Infuse the vinflunine over 20 minutes. Piggy-back the vinflunine infusion to the side injection port closest to the 500 mL NS or 5% glucose solution bag. This allows the vinflunine to be further diluted during administration.

5. Assess for patency frequently during the infusion,

6. Maintain extravasation precautions throughout the infusion.

7. After vinflunine infusion is completed (the line must be totally drained), run the remaining NS or 5% glucose solution bag at a flowing rate of 300 mL/hour (volume of at least 100 ml) for flushing the vein.

5.1.1.2. Anti-emetic and laxative prophylaxis

- Antiemetic prophylaxis will consist of a single dose of dexamethasone 8 mg or an equivalent dose of methylprednisolone just before each infusion.

- Administration of vinflunine requires addition of dietary measures and laxatives, to avoid potentially serious constipation, **starting the day of each vinflunine administration (day 1) to day 5 as follows:**

- Dietary measures including proper dietary fluid and fibre intake:
  - Oral hydration: at least 1.5 litres of water per day.
  - Diet containing high fibre foods (10 to 20 g of bran, whole-wheat breads and cereals or 5 fresh or cooked vegetables or fruits)
- Administration of laxatives listed below :
  - predominantly stool softener : lactulose, polyethylene glycol, docusate sodium, milk of

magnesium or mineral oil (paraffin)

- or predominantly stimulant : senna derivatives, cascara or bisacodyl.

Dose for laxatives are per investigator discretion. Use of other laxative treatment is allowed upon prior sponsor approval.

For patients considered at increased risk of serious constipation, defined as:

- ☐ History of chronic or refractory constipation,
- ☐ Concomitant treatment with opioids,
- ☐ Peritoneal carcinomatosis or abdominal tumour masses,
- ☐ Persistent symptoms under vinflunine despite the days 1 to 5 dietary measures and laxatives administration,

the use of a stool softener and a stimulant is recommended to maximise efficacy (Droney J, 2008).

Mouthwash is recommended as prophylaxis of stomatitis.

5.1.1.3. Methotrexate

Mouthwash is recommended as prophylaxis of stomatitis.

On day 1, methotrexate will be administered by direct bolus injection through the side arm of the remaining NS or 5% glucose solution bag after completion of vinflunine infusion.

On day 8, methotrexate will be administered though the side arm of a freely running NS or 5% glucose solution IV infusion.

5.1.2. Methotrexate (arm B)

Descriptions of study drug, storage, packaging, labelling and drug accountability are given in section 10.

Patients randomised to arm B will receive methotrexate on a weekly basis as a bolus intravenous injection at the dose of 40 mg/m²/week. The drug will be administered by direct injection through the side arm of a freely running NS or 5% glucose solution IV infusion.

One cycle of methotrexate is defined as a three-week period, i.e. 3 weekly administrations of methotrexate (days 1, 8, and 15).

5.2. GUIDELINES FOR TREATMENT MODIFICATIONS

Treatment will be modified in case of dose limiting haematological and/or non haematological toxicity. Dose adjustment and/or treatment delay are to be made according to the body system showing the greatest degree of toxicity. Toxicities will be graded according to the NCI Common Terminology criteria for Adverse Events (version 3.0).

5.2.1. General considerations

After any dose reduction, this dose is then maintained with no re-escalation of doses in subsequent cycles.

Re-treatment may be delayed by one week up to 2 weeks pending recovery. Any patient who requires a delay of more than 2 weeks, for whatever reason, will be taken off study.

In case of toxicity, all dosing adjustment or delay should be applied to both drugs of arm A unless there is another specific recommendation.

5.2.2. Vinflunine (arm A)

5.2.2.1. Dose modifications

Guidelines which have to be applied for dose modifications are detailed in Table 4.

The dose of i.v. vinflunine may be decreased depending on how well the patient tolerates the study drug. Dose of i.v. vinflunine will be reduced as described below.

Table 4: Dose reduction of IV vinflunine

Dose Level	Vinflunine
0 (starting dose)	280 mg/m²
-1	250 mg/m²
-2	225 mg/m²

Patients requiring dose reductions below dose level -2 must discontinue study drug with the following exception: patients with responding disease after consultation and approval by the sponsor.

5.2.2.2. Treatment modifications for haematological toxicity

Complete blood cell counts will be performed on days 1 and 8 of each cycle during the treatment period. If a patient experienced fever (temperature ≥ 38°C) and/or developed infection, blood cell count should be immediately performed.

Cycle delay

Cycle is considered delayed if Day 1 treatment has been performed:

- either ≥ 21 + 4 days since last Day 1 study drug administration (i.e., Day 26 or more).
- or ≥ 14 + 4 days since last Day 8 study drug administration

Neutrophil count should be ≥ 1.5 x 10^9/L (grade 1) and platelet count ≥ 100 x 10^9/L before each new cycle.

Table 5 details haematological toxicity which must result in cycle delay.

Table 5: Dose delay for haematological toxicity on day 1 of each cycle

Haematological toxicity on scheduled day 1			**Day 1 administration of study treatment**
Absolute neutrophils		Platelets	
ANC ≥ 1.5 x 10^9/L	And	≥ 100 x 10^9/L	No dose modification. Treat on time
ANC < 1.5 x 10^9/L	And/Or	< 100 x 10^9/L	Delay one week and reassess

If recovery has not occurred after a 2-week delay, the treatment will be discontinued unless approved by the sponsor.

Dose modifications

Table 6 details haematological toxicity which must result in dose reduction.

Table 6: Dose modifications for haematological toxicity

Haematological toxicity during the previous cycle	**Dose adjustment for next cycle**

Grade 3 thrombocytopenia (platelets $\geq$ 25 x 10^9/L and < 50 x 10^9/L) with significant bleeding or requiring transfusion	First appearance : decrease one dose level
Grade 4 thrombocytopenia (platelets < 25 x 10^9/L)	
Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting $\geq$ 5 days	Second appearance : decrease one dose level
Neutropenic infection (grade $\geq$ 3 neutropenia concomitant with grade $\geq$ 3 infection)	Third appearance : stop treatment
Febrile neutropenia of any grade	

5.2.2.3. Treatment modifications for non-haematological toxicity

Based on prior clinical experience of i.v. vinflunine, non-haematological adverse events which may require treatment modification include :

- nausea and vomiting
- constipation
- stomatitis
- and peripheral neuropathy.

Therefore, specific recommendations for treatment modifications for each of these adverse events are provided in this section.

Rare cases of Posterior Reversible Encephalopathy Syndrome (PRES) have been observed after administration of vinflunine. The typical clinical symptoms and signs are, with various degrees: neurological (headache, confusion, seizure, visual disorders), systemic (hypertension), and gastrointestinal (nausea, vomiting). Radiological signs are white matter abnormalities in the posterior regions of the brain. Clinical and radiological features usually resolved rapidly without sequelae after treatment discontinuation.

Vinflunine must be discontinued in patients who develop neurological signs of PRES.

Cycle delay

Rules defining the cycle delay are the same as outlined in section 5.2.2.2.

All non-haematological toxicity, except alopecia and fatigue should be resolved to grade ≤ 1 prior to starting a new cycle of treatment.

If grade ≥ 3 toxicity persists for more than 2 weeks, the study drug should be permanently discontinued.

Dose modifications

The table below outlines dose modifications for non-haematological toxicity.

Table 7: Dose modifications for non-haematological toxicity

Non haematological toxicity during the previous cycle	Dose adjustment for next cycle
Constipation	
Grade 2	Maintain treatment at the same dose Adjust laxative therapy*
Grade 3	Decrease one dose level Adjust laxative therapy*
Grade 4	Discontinue treatment
Stomatitis	
Grade 2	Maintain treatment at the same dose
Grade ≥ 3	Decrease one dose level
Peripheral neuropathy	
Grade 2	Decrease one dose level
Grade ≥ 3	Discontinue treatment
Other grade ≥ 3 toxicities**	To be adjusted as medically indicated after discussion between investigator and sponsor
Hyperbilirubinemia	
Grade 2 (> 1.5 x ULN ***and ≤ 3.0 x ULN)	Decrease dose to 250 mg/m²
Grade 3 (>3.0 x ULN)	Delay treatment until recovery to grade 2 and resume at 250 mg/m²
Decreased creatinine clearance (Cockroft-Gault)	
< 40 ml/min and ≥ 20 ml/min	Decrease dose to 250 mg/m²
< 20 ml/min	Discontinue treatment

* Give a stimulant and a stool softener
** Except grade 3 fatigue
*** Upper limit of normal

5.2.3. Methotrexate in Arm A

5.2.3.1. Dose modifications

The following dose levels will be used in modifying the dose of methotrexate in arm A:

Table 8: Dose reduction of methotrexate in Arm A

Dose level	Methotrexate
0 (starting dose)	30 mg/m²
- 1	20 mg/m²

Patients requiring dose reductions to less than 20 mg/m² must be discontinued with the exception of responding patients after consultation and approval by the sponsor.

5.2.3.2. Treatment modifications for haematological toxicity

Complete blood cell counts will be performed before each administration of methotrexate.

Cycle delay

Cycle is considered delayed if Day 1 treatment has been performed:

- either ≥ 21 + 4 days since last Day 1 study drug administration (i.e., Day 26 or more).
- or ≥ 14 + 4 days since last Day 8 study drug administration

Neutrophil count should be ≥ 1.5 x 10^9/L (grade 1) and platelet count ≥ 100 x 10^9/L before each new cycle (day 1 administration) as shown below.

Table 9: Arm A- Dose delay of methothrexate on day 1 for haematological toxicity

Haematological toxicity before day 1 administration			Day 1 administration of study treatment
Absolute neutrophils		**Platelets**	
ANC ≥ 1.5 x 10^9/L	and	≥ 100 x 10^9/L	No dose modification. Treat on time
ANC < 1.5 x 10^9/L	and / or	< 100 x 10^9/L	Delay cycle and reassess one week later

Dose delay / cancellation of methotrexate at day 8

If neutrophils count are < 1.5 x 10^9/L and/or platelets count < 100 x 10^9/L, the day 8 administration should be delayed 1 week, to day 15. If no recovery after reassessment one week later, the dosing should be cancelled (Table 10).

This protocol does not allow other cases of dosing delay of methotrexate. Any delay of a methotrexate dosing done outside of this above rule (also shown in Table 10) will be recorded as a delay and as a protocol deviation, (≥ 4 days with respect to the planned day).

Table 10: Dose delay or cancellation of methotrexate at Day 8 in Arm A

Haematological toxicity before administration			
Absolute Neutrophils		**Platelets**	**Day 8**
ANC ≥ 1.5 X 10^9/L	and	≥ 100 X 10^9/L	Treat on time
ANC < 1.5 x 10^9/L	and / or	< 100 x 10^9/L	Delay 1 week and reassess. If no recovery, dose must be cancelled

Dose modifications

Table 11 details severe haematological toxicity which must lead to dose reduction.

Table 11: Dose modifications of methotrexate for haematological toxicity in Arm A

Haematological toxicity after the previous administration	**Dose adjustment for next administration**
Grade 3 thrombocytopenia (platelets ≥ 25 x 10^9/L and < 50 x 10^9/L) with significant bleeding or requiring transfusion	First appearance : reduce one dose level Second appearance: stop MTX
Grade 4 thrombocytopenia (platelets < 25 x 10^9/L)	
Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting ≥ 5 days	
Neutropenic infection (grade ≥ 3 neutropenia concomitant with grade ≥ 3 infection)	
Febrile neutropenia of any grade	

5.2.3.3. Treatment modifications for non-haematological toxicity

The non haematological adverse events which may require treatment modifications include:

- stomatitis
- increased transaminases
- and less often, nausea, vomiting, diarrhoea and skin rash.

Cycle delay

Rules defining the cycle delay are the same as outlined in section 5.2.3.2.

Day 1 administration must be delayed in case of grade > 1 stomatitis or grade > 1 increase of transaminases (> 2.5 x ULN). Methotrexate must not be readministered before total recovery.

If recovery requires more than 2 weeks, methotrexate should be permanently discontinued.

Dose cancellation

Administration on day 8 must be cancelled in case of grade > 1 stomatitis or grade > 1 increase of transaminases (> 2.5 x ULN).

The protocol does not allow Day 8 dosing delay of methotrexate in case of non-haematological toxicity. Any delay of a methotrexate Day 8 dosing will be recorded as a delay and as a protocol deviation if it has been performed ≥ 7 + 4 days since last Day 1 study drug administration (i.e., Day 11 or more).

Dose modifications

The table below outlines dose reduction for non-haematological toxicity.

Table 12: Dose modifications of methotrexate in Arm A for non-haematological toxicities

Non haematological toxicity after the previous administration	Dose adjustment for next administration
Stomatitis Grade 1 Grade 2 Grade ≥ 3	 Maintain the same dose Decrease one dose level Discontinue MTX
Transaminases > 2.5 x ULN and ≤ 5.0 x ULN > 5.0 x ULN and ≤ 20 x ULN	 Decrease one dose level Discontinue MTX
Decreased creatinine clearance **(Cockroft-Gault)** ≤ 60 mL/min and ≥ 20 mL/min < 20 mL/min	 Decrease one dose level Discontinue treatment
Other grade ≥ 3* toxicities	To be adjusted as medically indicated

* except grade 3 fatigue

5.2.4. Methotrexate in Arm B

5.2.4.1. Dose modifications

The following dose levels will be used in modifying the dose of methotrexate:

Table 13: Dose reduction of methotrexate in Arm B

Dose level	Methotrexate
0 (starting dose)	40 mg/m²
- 1	30 mg/m²
- 2	20 mg/m²

Patients requiring dose reductions to less than 20 mg/m² must be discontinued with the exception of responding patients after consultation and approval by the sponsor.

5.2.4.2. Treatment modifications for haematological toxicity

Complete blood cell counts will be performed before each administration of methotrexate.

Cycle delay

Dosing is considered delayed if Day 1 treatment has been performed:

- either ≥ 21 + 4 days since last Day 1 study drug administration (i.e., Day 26 or more).
- or ≥ 14 + 4 days since last Day 8 study drug administration
- or ≥ 7 + 4 days since last Day 15 study drug administration

Neutrophil count should be ≥ 1.5 x 10^9/L (grade 1) and platelet count ≥ 100 x 10^9/L before each new cycle (day 1 administration) as shown below.

Table 14: Arm B - Dose delay of methotrexate on day 1 for haematological toxicity

Haematological toxicity before day 1 administration			**Day 1 administration of study treatment**
Absolute neutrophils		**Platelets**	
ANC ≥ 1.5 x 10^9/L	and	≥ 100 x 10^9/L	No dose modification. Treat on time
ANC < 1.5 x 10^9/L	and / or	< 100 x 10^9/L	Delay cycle and reassess one week later

If recovery has not occurred after a 2-week delay, the treatment will be discontinued unless approved by the sponsor.

Dose delay / cancellation of methotrexate at days 8 and 15

This protocol does not allow other cases of dosing delay of methotrexate. Any delay of a methotrexate dosing done outside of this above rule (also shown in Table 10) will be recorded as a delay and as a protocol deviation, (≥ 4 days with respect to the planned day).

The days 8 and 15 administrations should be cancelled if neutrophils count are < 1.5 x 10^9/L and/or platelet count < 100 x 10^9/L as shown below.

Table 15: Dose cancellation of methotrexate within a cycle in Arm B

Haematological toxicity before administration			**Arm B**	
Absolute Neutrophils		**Platelets**	**Day 8**	**Day 15**
ANC ≥ 1.5 X 10^9/L	and	≥ 100 X 10^9/L	Treat on time	Treat on time
ANC < 1.5 x 10^9/L	and / or	< 100 x 10^9/L	Dose cancellation	Dose cancellation

Dose modifications

Table 16 details severe haematological toxicity which must lead to dose reduction.

Table 16: Dose modifications of methotrexate in Arm B for haematological toxicity

Haematological toxicity after the previous administration	Dose adjustment for next administration
Grade 3 thrombocytopenia (platelets $\geq$ 25 x 10^9/L and < 50 x 10^9/L) with significant bleeding or requiring transfusion	First appearance : reduce one dose level Second appearance : reduce two dose levels Third appearance : stop treatment
Grade 4 thrombocytopenia (platelets < 25 x 10^9/L)	
Grade 4 neutropenia (ANC < 0.5 x 10^9/L) lasting $\geq$ 5 days	
Neutropenic infection (grade $\geq$ 3 neutropenia concomitant with grade $\geq$ 3 infection)	
Febrile neutropenia of any grade	

5.2.4.3. Treatment modifications for non haematological toxicity

The non haematological adverse events which may require treatment modifications include :

- stomatitis

- increased transaminases

- and less often, nausea, vomiting, diarrhoea and skin rash.

Cycle delay

Rules defining the cycle delay are the same as outlined in section 5.2.4.2.

Day 1 administration must be delayed in case of grade > 1 stomatitis or grade > 1 increase of transaminases (> 2.5 x ULN). Methotrexate must not be readministered before total recovery.

If recovery requires more than 2 weeks, methotrexate should be permanently discontinued.

Dose cancellation (days 8 and 15)

Administration on days 8 and 15 in arm B must be cancelled in case of grade > 1 stomatitis or grade > 1 increase of transaminases (> 2.5 x ULN).

This protocol does not allow other cases of dosing delay of methotrexate. Any delay of a methotrexate dosing done outside of this above rule (also shown in Table 10) will be recorded as a delay and as a protocol deviation, (≥ 4 days with respect to the planned day).

Dose modifications

The table below outlines dose reduction for non-haematological toxicity.

Table 17: Dose modifications of methotrexate in Arm B for non-haematological toxicities

Non haematological toxicity after the previous administration	Dose adjustment for next administration
Stomatitis Grade 1 Grade 2 Grade ≥ 3	 Maintain the same dose Decrease one dose level Decrease two dose levels
Transaminases > 2.5 x ULN and ≤ 5.0 x ULN > 5.0 x ULN and ≤ 20 x ULN	 Decrease one dose level Decrease two dose levels
Decreased creatinine clearance (Cockroft-Gault) ≤ 60 mL/min and ≥ 20 mL/min < 20 mL/min	 Decrease one dose level Discontinue treatment
Other grade ≥ 3* toxicities	To be adjusted as medically indicated

* except grade 3 fatigue

5.2.5. Discontinuation of vinflunine or methotrexate in Arm A due to toxicity

Patients in arm A who require discontinuation of methotrexate may remain on vinflunine alone for the remainder of the study. Likewise, patients who require discontinuation of vinflunine may remain on methotrexate alone for the remainder of the study.

The patients who require discontinuation of methotrexate must continue with vinflunine at the current dose level for at least one more cycle. For patients who require discontinuation of vinflunine, methotrexate dosing must be increased to 40 mg/m² for at least one more cycle. Thereafter,

- if toxicity subsequently occurs, that requires treatment modifications of methotrexate, rules described in Arm B should apply (Table 16, Table 17).

5.3. TREATMENT ASSIGNMENT

Patients will be randomised after written informed consent is obtained, all screening assessments (see

Table 18, Section 7.1) are performed and the health-related quality of life questionnaire is completed.

The investigator will determine a patient to be eligible and will enroll him/her by contacting the independent central registration center (either Interactive Voice Response System, IVRS, or Interactive Web Response System, IWRS).

Randomisation will be stratified according to a minimisation procedure (Pocock SJ, 1975) set up by the independent central registration centre, on the following factors:

- WHO performance status (0 versus 1)

- Refractory or resistant to platinum versus other

- Prior radiotherapy (yes versus no)

- Prior treatment with any anti-EGFR medication (yes versus no)

- Center

Randomisation and registration procedures are described in Section 7.2.

Patients withdrawn from the study retain their number. New patients must always be allotted a new patient number.

5.4. DURATION OF TREATMENT

Patients will receive at least 2 cycles of study drug unless there is disease progression or unacceptable toxicity. After the first 6 weeks of study treatment, tumour response will be assessed : patients who respond or have stable disease will receive 2 additional cycles and will be reevaluated for tumour response. Patients with progressive disease will be removed while patients who respond or have stable disease will continue study treatment until disease progression.

In case of documented progression occurring before the first disease evaluation (6 weeks), the treatment will be discontinued and the response to treatment will be defined as early progression.

6. CONCOMITANT MEDICATIONS

All treatments given in addition to the study treatment at baseline and/or during the study are regarded as concomitant treatments and will be documented on the appropriate forms of the CRF / eCRF.

6.1. PROHIBITED TREATMENTS

6.1.1. Arms A and B

- Concomitant use of yellow fever vaccine is contraindicated due to the risk of fatal generalized vaccinal disease. Concomitant use of live attenuated vaccines is not recommended due to the risk of systemic, possible fatal disease.

- Patients must not receive any other anticancer treatment while on study.

- During the study and within 30 days following the last study drug dosing the patient will not participate in another study.

- In combination with methotrexate, the following medications are prohibited :

- phenylbutazone

- indometacine

- phenytoine

- salicylates (used at antalgic, anti-pyretic or anti-inflammatory doses)

- trimethoprim

- and probenecid

6.1.2. Arm A

Strong inhibitors of the cytochrome P450 isoform 3 A4 (CYP3A4) are prohibited during study treatment, especially ketoconazole and ritonavir. A non-exhaustive list of inducers or inhibitors of CYP3A4 is provided in Appendix 8. Concomitant use of CYP3A4 inhibitors or inducers should be avoided during the treatment period since they could alter systemic exposure to vinflunine (IRPF CSR CA 18 3009).

6.1.3. Arm B

Cross-over to vinflunine is prohibited.

6.2. RESTRICTED TREATMENT

6.2.1. Arm A

Caution is warranted when administering vinflunine to patients taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. Systemic exposure to these medications could be increased while receiving vinflunine.

Even if no data is available, the opposite impact to that from inhibitors (that is decrease in vinflunine blood levels) may be anticipated. Concomitant **CYP3A4 inducers** should be avoided (list provided in Appendix 8), if possible, since they could alter the systemic exposure to vinflunine.

The use of concomitant medications that prolong the QT/QTc interval should be avoided (list provided in *http://crediblemeds.org/everyone/composite-list-all-qtdrugs/?rf=All*).

6.2.2. Arm A and B

The concomitant use of non steroidal antiflammatory drugs including selective inhibitors of cyclooxygenase 2 and penicillin is not recommended because those drugs can decrease the renal clearance of methotrexate.

6.3. AUTHORISED TREATMENTS

- In the two study arms :

  - ancillary treatments will be given as medically indicated: antiemetics, antidiarrhoeals, antibiotics etc

  - analgesics (if opioids are given, laxative prophylaxis should be adapted in the vinflunine arm (arm A) according to section 5.1.1.2)

  - localized palliative radiotherapy will be allowed if the irradiation concerns less than 10% of the bone marrow reserve (see Appendix 3)

  - prophylactic or therapeutic use of G-CSF will be permitted according to institutional guidelines.

  - erythopoietin according to institutional practice

  - nutritional support

7. PLAN OF THE STUDY

Written informed consent will be obtained from the patient before any study specific procedure is undertaken. Patients will be informed about the study, both verbally and by reviewing the patient information sheet and consent form. The patient must be given the opportunity to ask questions and be given time to consider his/her participation. The investigator and the patient will both sign and personally date the consent form as confirmation of consent.

Following the amendment PA11, the addendum to the informed consent will be signed by all patients (under treatment or in follow-up).

7.1. SCREENING PERIOD

The screening period is the time preceding randomization and includes the 21-day period for performing screening assessments.

Table 18: Study procedures during the screening period

Study screening procedure	Timing – Comments
Written informed consent	To be obtained and signed both by the patient and the investigator prior to any study specific procedure
Demography, medical history, diagnosis and prior therapy	To be done once at baseline
Serum or urine pregnancy test in women of childbearing potential	Test within **72 hours** prior to the first study treatment.
TUMOUR ASSESSMENT - Cervical CT-Scan or MRI (1) - Chest / upper abdominal CT-Scan or MRI (1) - Other imaging if necessary (3)	Mandatory assessments are to be performed within 21 days prior to the first study treatment.
SAFETY ASSESSMENTS - Electrocardiogram - Laboratory test (2)	Within 7 days prior to first study treatment
PHYSICAL EXAMINATION Height, weight, blood pressure and pulse, temperature, performance status (WHO score)	Within 7 days prior to first study treatment
SYMPTOMS / CONCOMITANT TREATMENTS	Within 2 weeks prior to first day of treatment
Health-related QUALITY OF LIFE (EORTC QLQ-C30 and QLQ H & N 35 questionnaires)	To be obtained before randomisation (within 24 hours)

(1) Chest CT-scan must include the supraclavicular area

(2) Haematology: complete blood count. Serum chemistry: transaminases, alkaline phosphatase, total bilirubin, total protein, albumin, urea, creatinine and calculated (Cockroft-Gault) creatinine clearance, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate

(3) Bone scintigraphy, brain CT-scan or MRI, etc

7.2. ASSIGNMENT OF SCREENING NUMBER

For any patient screened, the site will assign a unique screening number which cannot be reused for any reason. Patient who have completed all specified baseline screening procedures and satisfy all the inclusion/exclusion criteria may be proposed for randomisation. For each site, a patient screening log is to be completed with the patient's screening number and the registration number, assigned by the randomisation if the patient is registered. If a patient is not registered, the reason for exclusion from the study will be recorded in this log.

7.3. STUDY ENTRY

Randomisation will be performed by using Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS).

Once written consent has been given by the patient, all inclusion/exclusion criteria must be checked by the investigator in order to confirm eligibility, prior to IVRS (or IWRS) randomisation procedure. The following information will be required when the investigator calls the IVRS or logs in IWRS for patient enrolment:

- study code,
- personal user access number and secret code
- institution name, investigator's name and country
- patient's birth date (day/month/year)
- answers to the questions relating to the stratification factors
- patient's eligibility.

The IVRS / IWRS will randomly assign the patient to one of the two treatment arms and will allocate the patient a registration number that will be communicated to the investigator. In parallel, the sponsor will receive this registration number as well as any information submitted by the investigator during the randomisation procedure.

The patient number will have six digits. The first two digits identify the country; the third and fourth, the centre; and the last two digits the patient within the centre. This patient registration number must be reported on all CRF pages and in any study document. A patient who has not been randomised and registered before the first administration will not be accepted for the study at a later date.

Randomisation is the starting point of the study, it is mandatory not to exceed an interval of 1 week between the date of registration and the start of the study treatment. In any case, all events occurring after registration must be recorded in the CRF /eCRF and will be taken into account in the analysis, whether the patient received the study treatment or not.

7.4. EVALUATION DURING THE STUDY PERIOD

The treatment period begins on the day of randomisation and continues until 30 days after the last study treatment administration.

The following assessments need to be completed throughout the treatment period:

Table 19: Assessments during the treatment period

Assessments	Timing - Comments
PHYSICAL EXAMINATION including weight, blood pressure and pulse, temperature, performance status (WHO score)	To be performed at day 1 of each cycle.
REVIEW OF SYMPTOMS, TOXICITY AND TREATMENTS	To be performed at day 1 of each cycle. All clinical findings and results from any complementary examination should be recorded in the CRF / eCRF.
LABORATORY TESTS (1)	
Haematology	- To be performed within 24 hours on days 1 and 8 of each cycle in arm A and before each weekly administration in arm B - In case of fever or infection according to institutional standards and investigator decision.
Serum chemistry	- To be performed within 24 hours before day 1 of each cycle in both arms (except glucose, total protein and albumin every 6 weeks)
ECG	- To be performed on D1 of the first cycle before and after drug administration in both arms and then every two cycles in both arms
TUMOUR ASSESSMENT (2)	To be performed every 6 weeks (+/- 3 working days) from randomisation (regardless of the timing of treatment cycles). All sites identified at baseline must be evaluated at each tumour assessment.
Health-related QUALITY OF LIFE (EORTC QLQ-C30 and QLQ H & N 35)	To be assessed every 6 weeks

(1) Haematology: complete blood cell count.
Serum chemistry: transaminases, alkaline phosphatase, total bilirubin, total protein, albumin, urea, creatinine and calculated (Cockroft-Gault) creatinine clearance, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate

(2) Tumour assessment: all target lesions (measurable disease) and non-target lesions (non-measurable disease) found at baseline should be re-investigated at each tumour assessment. Additional examinations may be performed if appearance of new lesions is suspected.

- Only the lesions found at baseline must be re-investigated. The same methods of assessment used at baseline should be used throughout the study to ensure comparability (*i.e.* scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and preferably the same scanner).

- Lesions on chest X-rays are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung.

- Ultrasound is not an acceptable method to measure disease.

- All adverse events which occurred during the cycle must be assessed and documented using the CTCAE version 3.0.

- ECG to be performed on day 1 of cycle 1 before and after drug administration in both arms. Thereafter, ECG will be performed before drug administration every 2 cycles in both arms. After review of safety data including ECG results by the IDMC, the need for repeated ECGs before each cycle can be revised. In case of QT/QTc > 500 msec (grade 3), patients should be hospitalized for a close and continuous ECG monitoring until cardiology consultation.

- Concurrent prescriptions, blood products, palliative radiotherapy must be documented.

7.5. END-OF-STUDY PERIOD EVALUATION

Clinical workup to be performed within 30 days after last administration of study drug as detailed below.

Table 20: Assessment at the end of study treatment

Assessments	End of study treatment evaluation
PHYSICAL EXAMINATION: including weight, blood pressure, pulse, temperature, performance status (WHO score)	To be performed within 30 days after discontinuation of study drug.
REVIEW OF SYMPTOMS, TOXICITIES AND TREATMENTS	To be performed within 30 days after discontinuation of study drug(1). All clinical findings and results from any complementary examination should be recorded in the CRF / eCRF.
LABORATORY TESTS	
Haematology(2) and serum chemistry(3)	To be performed within 30 days after discontinuation of study drug.
TUMOUR ASSESSMENT(4)	Patients who discontinued protocol treatment for other reason than disease progression have had tumour assessments every 6 weeks from time of randomisation until revised RECIST guideline (version 1.1) criteria for

	progressive disease have been met. All sites identified at baseline had to be evaluated at each tumour assessment. **At the time of the amendment PA11, no further assessments will be performed after the end of study treatment evaluation period.**
Health-related QUALITY OF LIFE (EORTC QLQ-C30 and QLQ H & N 35)	To be performed within 30 days after discontinuation of study drug.

(1) All AEs (except alopecia and fatigue) related to the study drug will be followed until recovery or return to the baseline status or grade 1 or until start day of a new anticancer therapy.
(2) Haematology: complete blood cell count.
(3) Serum chemistry: transaminases, alkaline phosphatase, total bilirubin, total protein, albumin, urea, creatinine, and calculated (Cockroft-Gault) creatinine clearance, glucose, calcium, sodium , potassium, magnesium, chloride, bicarbonate.
(4) Additional examination may be needed if appearance of new lesions is suspected.

The patient must not participate into another study of an investigational drug during the 30 days after study drug discontinuation.

7.6. PREMATURE DISCONTINUATION

A patient may voluntarily discontinue his/her participation in this study at any time. The investigator may also, at his or her discretion, discontinue the patient from participating in this study at any time. If a patient is prematurely discontinued for any reason, the investigator must make every effort to perform the assessments as outlined in Section 7.5 end-of-study treatment evaluation. These data should be recorded, as they comprise an essential evaluation that should be done prior to discharging any patient from the study.

In the event that a patient is prematurely discontinued from the study at any time due to an adverse event (AE) (as defined in Section 9.1) or a serious adverse event (SAE) (as defined in Section 9.2), the procedures stated in Sections 9.1 and 9.2 must be followed.

The primary reason for withdrawal will be clearly documented in the subject's medical record and recorded in the CRF / eCRF. A final evaluation will be completed at the time of discontinuation for the study (see Section 7.5). Study treatment must be immediately discontinued for the following reasons:

- Disease progression: any patient who experiences disease progression. The patient will be withdrawn from the study and reported as a progression for the final evaluation.

- The investigator's decision in the patient's interest. Particularly, if a serious adverse event occurs and is considered by the investigator liable to threaten the health of the patient or if a

serious disease occurs and necessitates the prescription of a medication incompatible with the pursuit of the study. The study clinical manager (monitor) will be informed by phone or fax and the investigator will complete the SAE notification form (Appendix 5) to be forwarded to the monitor as soon as possible.

- An erroneous inclusion according to the protocol. The decision to maintain or not the patient in the study will be taken jointly by the investigator and the sponsor.

- Patient compliance: any significant non-medical deviation from the protocol

- Investigator non-compliance: any significant medical or non-medical deviation from the protocol

- A patient who wishes to stop the study treatment may do so at any time but must inform the investigator. In this case, the investigator should attempt to contact the patient as soon as possible for a final assessment in order to: i) evaluate the patient's clinical condition, ii) if necessary, take the appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.

- A patient who wishes to withdraw his/her consent from the study participation for any reason may do so at any time but must inform the investigator. In this case, the investigator should attempt to contact the patient as soon as possible for a final assessment in order to: i) have the patient's decision written in the consent form, ii) obtain the reason for withdrawal and report it in the CRF / eCRF, iii) evaluate the patient's clinical condition, iiii) if necessary, take the appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment.

- Any other reason to be documented.

All patients who have received at least one dose of study drug will be evaluable for safety analysis. In all cases, available data will be retained for the safety analysis.

7.7. FOLLOW-UP PERIOD ASSESSMENT

The follow-up period was initially defined as the time from 30 days after the last study treatment administration (last administration of the last study drug administered) until death.

For patients randomised to arm B (methotrexate), cross-over to vinflunine was prohibited.

1- For patients who discontinued the study treatment before the occurrence of disease progression.

Clinical and radiological assessments of all lesions had to be performed every 6 weeks from time of randomisation until disease progression was documented in addition to survival information listed below.

2- For patient who discontinued the study treatment due to PD.

Survival information had to be collected approximately every month for the first 6 months and then every 3 months until death.

Had to be recorded:

- Date last known to be alive and WHO score.
- If deceased, date, place and cause of death, source of information and performance or not of an autopsy.
- Date and type of subsequent anti-cancer therapy and best response to this therapy.

At the time of the amendment PA11, there will be no more follow-up period for this study.

8. MEASUREMENTS AND EVALUATION

8.1. EFFICACY ASSESSMENT

8.1.1. Overall survival

The main endpoint of this study is overall survival defined as the time from randomisation to the date of death or last follow-up. For patients who have not died, survival duration will be censored at the date of last contact or last follow-up.

8.1.2. Evaluation of tumour response

The same methods of assessment and the same technique should be used at baseline and throughout the study to ensure comparability (*i.e.* scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent and preferably the same scanner). Imaging-based evaluation is preferred to evaluation by physical examination when both methods can be used to assess a lesion. CT-scan and MRI are preferred. If not available, sequential CT-scan could be used. IV contrast should be used for all patients, unless contraindicated. All anonymised images (coded identification of patients) must be duplicated, either as CD rom or original films performed at the same time as those performed for the investigator, in order to be made available for the sponsor only upon request. They could be used for an independent review.

Ultrasound should not be used to measure tumour lesions.

The clinical response will be determined using the revised RECIST guideline version 1.1 (Therasse P, 2000, Eisenhauer E, 2009).

Lesions are categorised into one of the two following groups for the purposes of response analysis **measurable and non-measurable** lesions. All the measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total will be measured every 6 weeks and will be considered as “target lesions”. All the other lesions (non target measurable lesions and non-measurable lesions) will be regularly assessed as present or absent or unequivocal progression.

8.1.2.1. Disease measurability

- **Measurable lesions**

Tumour lesions must be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of :

- 10 mm by CT-scan (CT-scan slice thickness no greater than 5 mm)

- 10 mm caliper measurement by physical examination

- 20 mm by chest x-rays, sequential CT-scan or MRI

Lymph nodes are defined as measurable if their short axis is ≥ 15 mm by CT-scan. (CT-scan slice thickness recommended to be no greater than 5 mm).

These lesions will be identified as **target lesions** and will be recorded and measured at baseline.

CT-scan is the best currently available and most reproducible method for measuring target lesions.

Irradiated tumour lesions will not be eligible for measurable disease while lesions appearing in a previously irradiated area will be considered as measurable lesions.

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However if non-cystic lesions are present in the same patient, they will be preferred as target lesions.

Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT-scan or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- **Non-measurable lesions**

Non-measurable lesions are all the lesions other than measurable lesions, including small tumour lesions (longest diameter < 10 mm with CT-scan or < 20 mm with conventional techniques and

MRI), pathological lymph nodes with short axis ≥ 10 mm but < 15 mm by CT-scan as well as truly non-measurable lesions.

Lesions that are considered as truly non-measurable include the following :

- Lytic bone lesions or mixed lytic-blastic lesions without identifiable soft tissue components and blastic bone lesions
- Leptomeningeal disease
- Ascites
- Pleural / pericardial effusion
- Lymphangitis cutis / pulmonis
- Abdominal masses / organomegaly identified by physical examination that is not measurable by reproducible imaging techniques

All these lesions will be identified as **non-target lesions**. Their measurements are not required and these lesions will be followed as **"present"** or **"absent",** or in rare cases **"unequivocal progression"**.

8.1.2.2. Criteria for evaluation

♦ **Target lesions**

The evaluation of target lesions will be performed using the sum of the diameters (longest for tumour lesions, short axis for lymph nodes) for all these lesions. If lymph nodes are to be included in the sum, then, as noted above, the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise the objective tumour response of the measurable dimension of the disease as follows :

- Complete Response (CR) : disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

- Partial Response (PR) : at least a **30% decrease** in the sum of diameters of target lesions taking as reference the baseline sum diameters.

- Progression (PD) : at least a **20% increase** in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note that the appearance of one or more lesions is also considered as a progression.

- Stable Disease (SD) : neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum diameters while on study.

♦ **Non target lesions**

The evaluation of non-target lesions will be as follows :

- Complete Response (CR): disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR / Non-PD: persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

- Progression (PD): appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions such as increase in a pleural effusion from “trace” to “large”, increase in lymphangitic disease from localised to widespread.

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden on the basis of non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, i.e. an increase in tumour burden representing an additional 73% increase in volume (which is equivalent to a 20% increase diameter in a mesurable lesion).

8.1.2.3. Best overall response

The best overall response is determined once all the data for the patient are known.

Best overall response is defined as the best response across all time points.

Determination of the overall response in case of presence of target lesions with or without non-target lesions is detailed in Table 21. For patients with non-target lesions only, determination of the overall response is given in Table 22.

Table 21: Time point response: patients with target (+/- non target) disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR / Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-target tumour lesions including pleural effusion, ascites, lymphangitis and/or bone lesions which are not associated with symptom appearance or symptom worsening will not disqualify a response reported on target lesions if they are not evaluated.

Non target lymph nodes must be evaluated to document a response reported on target lesions.

In those patients who had bone lesions at study entry, non target bone metastases must be evaluated (bone scintigraphy) to document an overall complete response.

Table 22: Time point response: patients with non target disease

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR / Non-PD	No	Non-CR / Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

8.2. SAFETY ASSESSMENT

8.2.1. Clinical safety

The following tests will be performed prior to and on specified days during and following therapy:

- Complete history of malignant and non-malignant diseases,
- Full physical examination including vital signs, weight, assessment of performance status,
- ECG at baseline, and throughout the study treatment: on day 1 of cycle 1 before and after drug administration in both arms and then before drug administration every 2 cycles in both arms. After review of safety data including ECG results by the IDMC, the need for repeated ECGs before each cycle can be revised.
- Regular collection of adverse events and graded according to CTCAE version 3.0.

8.2.2. Laboratory investigations

The following tests will be performed according to study flow chart:

- Complete blood cell counts,
- Serum chemistry: transaminases, alkaline phosphatase, total bilirubin, total protein, albumin, urea, creatinine and calculated (Cockroft-Gault) creatinine clearance, glucose, calcium, sodium, potassium, magnesium, chloride, bicarbonate.

8.3. PHARMACOKINETICS

Not applicable in this study.

8.4. QUALITY OF LIFE

- During the course of the study, the patients will be asked to complete the QLQ-C30 questionnaire and the QLQ-H & N 35 module to measure the health-related quality of life.

Support for the reliability and validity of the QLQ-C30 questionnaire and the QLQ H & N 35 module has been reported in the published literature.

- The QLQ-C30 questionnaire and the QLQ-H & N 35 module will be completed prior to randomisation (within 24 hours), every 6 weeks and at the end of treatment evaluation.

- Patients will be considered evaluable for health-related quality of life analysis if they have completed at least 2 questionnaires (including the questionnaire completed within 24 hours prior to randomisation). Of note, if local language is not available the patient will not be evaluable.

8.5. PHARMACOECONOMICS

Data concerning chemotherapy (cycle, dose etc…), setting for chemotherapy, antiemetics, concomitant medication, material used (central venous line), adverse events, hospitalisations, consultations during chemotherapy, will be collected in order to perform a pharmaco-economic assessment (as a piggy-back study) of study treatments. Data will be collected in the CRF / eCRF.

8.6. COMPLIANCE

The administration of study treatment must be done in the investigational centre and supervised by a physician or a nurse of the department. For each patient, the investigator is responsible for dispensing the study medication delivered by the Institut de Recherche Pierre Fabre or its representative in accordance with the protocol (see Section 10.3).

9. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

9.1. ADVERSE EVENTS

9.1.1. Definition

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign

(including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH-Guideline for GCP).

All laboratory tests for which abnormal results are collected after the initiation of study treatment should be repeated until the values return to normal or to stable status. Abnormal results are defined as those falling out of the laboratory normal range that are clinically significant. The frequency with which such checks should be made will be defined at the investigator's opinion depending on the degree of abnormality.

In all cases, the aetiology should, as much as possible, be identified and the sponsor notified.

9.1.2. Grading of adverse events

The severity of adverse events should be determined using NCI CTC AE version 3.0.

9.1.3. Reporting of adverse events

Any adverse or intercurrent event occurring during the study period, spontaneously reported by the patient or observed by others, will be recorded in the CRF, either in paper or electronic version. Haematology and biochemistry adverse events will be extracted from the laboratory forms of the CRF. However, in case they result in seriousness and/or corrective treatment, and/or study drug treatment modifications and/or discontinuation, they will also be reported in the Pre-treatment or Adverse Events Form of the CRF.

The records will describe the nature (diagnosis, signs and symptoms), severity, date/time of onset, date/time of end, outcome and actions taken, and relationship to study treatment (according to the investigator's opinion).

It will be specified whether the event is serious or not.

AEs already recorded and designated as "continuing", should be reviewed at each subsequent assessment. If resolved, the details in the CRF / eCRF are completed. If any AE changes for the worse, in frequency of attacks/symptoms or in severity, a new record of the event must be started

(*i.e.* distinct reports are required for differing frequencies and/or severity of the same event to enable comprehensive safety reports and later analysis).

9.2. SERIOUS ADVERSE EVENTS

9.2.1. Definition of SAE

A serious adverse event (SAE) includes, but is not necessarily restricted to, any event which:

- results in death (whatever may be the cause),
- is life-threatening,
- results in persistent or significant disability/incapacity,
- requires patient hospitalisation or prolongation of existing hospitalisation,
- is a congenital anomaly or birth defect,
- other events including cancer, overdosage, pregnancy and any additional adverse experience or abnormal laboratory values occurring during the study period defined by the protocol as serious or which the investigator considers significant enough or that suggests a significant hazard, contraindications, side effect or precaution will be handled as a serious adverse event.

Any overdosage meeting a seriousness criteria should be reported as a SAE as described in § 9.3.

Any pregnancy occurring after patient exposure to study drug, should be reported on the SAE notification form as described in Section 9.4.

Any hospitalisation, or prolongation of hospitalisation due to the circumstances listed below, will not be reported as SAE :

- Planned (as per protocol) medical/surgical procedure, including central venous line (CVL) setting

- Preparation for routine health assessment/procedure (e.g. routine colonoscopy),

- Planned medical/surgical admission (planned prior to entry into study trial, appropriate documentation required),

- Administrative or social reasons (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances),

- New treatment of the disease within 30 days after the last study drug administration

All deaths occurring while the patient is on study including deaths due to disease progression and deaths within 30 days of last administration of study drug should be notified as SAE.

Unexpected adverse drug reaction is defined as:

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: definitions and standards for Expedited Reporting).

9.2.2. Reporting of SAE

All serious adverse events occurring during treatment and 30 days after the last study drug administration, according to the above-mentioned definitions, regardless of treatment or relationship to study drug, must be recorded by the investigator as soon as he/she is informed of the event.

The investigator must notify the sponsor of this event by sending within 24 hours the "Notification of serious adverse event" form (initial report Appendix 5) with all the available information concerning the event, including the causality assessment, to : Pierre Fabre Corporate Vigilances Division, by email to: HQ.pharmacovigilance@pierre-fabre.com or by fax: + 33 (0) 1.49.10.80.90.

9.2.3. Follow-up of SAE

Any serious and/or unexpected adverse event should be medically well documented and the information should be available as soon as possible.

The investigator must draw-up a special clinical report and use the "Notification of serious adverse event" form ("follow-up") and collect the results of the carried out examinations and the reports of hospitalisation.

The serious adverse events must be followed up until resolution or stabilisation.

9.2.4. SAE occurring after the study

Any SAE occurring during 30 days following the last study drug administration for the subject should be notified to the sponsor.

Should also be notified to the sponsor any event occurring at any time after the end of the study treatment for the subject that may be related to the study treatment according to the investigator's opinion.

9.2.5. Sponsor's responsibilities for safety reporting purposes

Sponsor will submit expedited and periodic reports to both Competent Authorities and Ethics Committees per corporate standard operating procedures as regards to the EU directive 2001/20/EC taking into account local specific requirements. The reference documents for each study drug will be last version in force (IB, SPC). Indeed, these reference documents are likely to be updated during the study.

9.3. REPORTING OF OVERDOSAGE TO THE SPONSOR

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important.

The main toxic effect due to an overdose of vinflunine is bone marrow suppression with a risk of severe infection.

Medical management of overdose should include customary therapeutic and supportive medical interventions aimed at correcting the presenting clinical manifestations and preventing their possible complications.

In the absence of seriousness criteria, the overdosage and associated adverse event if any are only reported on the AE page of the CRF / eCRF. If the definition of seriousness criteria is met, the SAE notification form must be completed and transmitted to the sponsor.

9.4. REPORTING OF PREGNANCY TO THE SPONSOR

Pregnancies discovered in the period in between the informed consent form signed but before any study drug exposure are not to be reported to the sponsor unless associated to a seriousness criteria (e.g. serious adverse event study-protocol related procedure). If pregnancy is confirmed, the women must not be administered the study drug(s) and be withdrawn immediately from the study.

If pregnancy is suspected while the subject is receiving study treatment, the study drug should be discontinued immediately until the result of the pregnancy testing is known. If pregnancy is confirmed, then the study treatment is permanently discontinued in an appropriate manner. The investigators must report to the sponsor any pregnancy which occurs during or after the patient exposure to the study drug and until 3 months after the last study drug administration. The investigator must immediately notify the monitor using the SAE notification form and also report the pregnancy on the AE page of the CRF / eCRF.

Women who become pregnant during or after exposure to the study drug must be followed by the investigator until the completion / termination of the pregnancy. If the pregnancy goes to term, the outcome will have to be reported to the sponsor (baby's healthy status) as a follow-up using the SAE notification form.

10. CLINICAL PHARMACY

10.1. PHARMACEUTICAL INFORMATION

10.1.1. Pharmaceutical information of vinflunine

10.1.1.1. Drug supply

"Pierre Fabre Medicament" represented by "Institut de Recherche Pierre Fabre" will supply i.v. vinflunine to each investigational centre.

Drug substance name

- Recommended INN : vinflunine ditartrate
- Chemical name (4'R) - 20', 20'-difluoro 3'4'-dihydrovinorelbine L -(+) - tartrate (1 : 2)

Drug product name

- Commercial name: JAVLOR®.

Pharmaceutical forms

Presentation: type I colourless glass vial containing concentrate for solution for infusion of vinflunine:

- 50 mg / 2mL
- 250 mg / 10 mL.

Vinflunine must be diluted for administration.

Composition: vinflunine ditartrate 68.35 mg corresponding to vinflunine (base) 50.00 mg and water for injection q.s.f. 2 mL or vinflunine ditartrate 341.75 mg corresponding to vinflunine (base) 250.00 mg and water for injection q.s.f. 10 mL.

10.1.1.2. Storage

- The expiry date is indicated on the labels of the container and vials.
- Store in a refrigerator (+2° C to +8° C) protected from light in original closed container.

- Do not freeze.
- The stability study allows shipment (not more than 7 days) at temperature up to 30° C protected from light in the original closed container.
- After dilution of product in polyethylene or polyvinyl chloride infusion bag, administration has to be undertaken within 24 hours when stored in the refrigerator (+2°C/+8°C) protected from light. If the product is exposed to light, administration has to be undertaken within one hour.

10.1.2. Pharmaceutical information of methotrexate

10.1.2.1. Drug supply

Methotrexate will be supplied directly by "Pierre Fabre Medicament" represented by "Institut de Recherche Pierre Fabre" to each investigational centre.

10.1.2.2. Storage

See on the outer packaging. The expiry date is indicated on the labels of the container.

10.2. PACKAGING AND LABELLING

10.2.1. Packaging and labelling of vinflunine

10.2.1.1. Packaging

Vinflunine concentrate for solution for infusion is available in sealed polystyrene box with 10 single-dose vials of vinflunine 50 mg / 2ml or 250 mg / 10 ml each.

10.2.1.2. Packaging use

Vinflunine must be used vial per vial for all patients according to dosage as given in Section 5.1.1. Each vial is for single use only.

10.2.1.3. Study drug labelling

The labels will be in accordance with European Good Manufacturing Practices and the local requirements where the study is to be conducted.

- Each box and each vial are labelled with information shown in Appendix 4 (i.v. vinflunine 50 mg / 2ml and 250 mg / 10 ml).
- One tear-off part label of each vial has to be stuck by the person in charge of dispensing (hospital pharmacist or investigator) on the appropriate drug accountability form (Appendix 6).
- Additional documentation will be added in accordance with regulatory requirements if necessary.

10.2.2. Packaging and labelling of methotrexate

The labels will be in accordance with European Good Manufacturing Practices and the local requirements where the study is to be conducted.

Methotrexate is available in vials of 50 mg / 2 ml.

Methotrexate must be used vial per vial for all patients according to the dose given in section 5.1.2. Each vial is for single use only.

Each box and each vial are labelled with information shown in Appendix 4.

One tear-off label of each vial has to be stuck by the person in charge of dispensing (hospital pharmacist or investigator) on the appropriate drug accountability form (Appendix 6).

Additional documentation will be added in accordance with regulatory requirements if necessary.

10.3. ON SITE DRUG ACCOUNTABILITY AND DISPENSING

Study drug supply will be performed by the IVRS (or IWRS) according to the procedures described in a user manual which will be given to the investigational centre personnel. Each person accessing

the IVRS / IWRS system will be assigned an individual unique access number as detailed in a specific charter (see section 5.4).

The hospital pharmacist or investigator are responsible for adequate storage of the study medication according to the manufacturer recommendations and for dispensing the treatment to the patients. The study medication must be used in accordance with the protocol and only by the Investigator.

The investigator and/or pharmacist must maintain adequate and accurate records, showing the receipt, storage and distribution of all supplies of the study medication delivered by the Institut de Recherche Pierre Fabre.

These records include:

- All the accompanying letters, which list the batch number of the medication, the quantities received, and the date of reception;
- The Drug Accountability Forms (see Appendix 6) which include the patient's identification, the date of dispensation, each quantity dispensed, and the identification of the dispenser. The original will be kept by the Sponsor and the copies will be left on site: one in the pharmacist's file and one in the investigator's file;
- A summarized document entitled "Accountability of investigational products on site" which describes all the movements of investigational products during the trial. The original will be left in the pharmacist's file and the copies in the study file, and in the investigator's file.

When necessary, study drug can be ordered by calling the IVRS (or logging in the IWRS).

10.4. RECALL OF INVESTIGATIONAL PRODUCTS

In case of recall of investigational products (decided by the Competent Authorities or the sponsor), the investigator will be immediately informed by the sponsor.

The investigator, in collaboration with the sponsor representatives (monitor, CSC) must urgently stop the delivery of the concerned investigational products to the patients.

The monitor / CSC in collaboration with the Clinical Pharmacy Department organizes the return of the recalled products to the sponsor drug supply unit, according to the sponsor procedures.

10.5. UNUSED DRUG AND DESTRUCTION

Unused trial medications have to be kept by the investigator or returned to pharmacist. All unused drugs must be either destroyed or returned to the sponsor. Destruction will be performed according to both sponsor and investigator centre procedures and after checking by the local CRA. It is the Investigator's or pharmacist's responsibility to insure that the study medication used by the subjects plus the left over unused study medication equal the total amount received from the Sponsor. Any discrepancy should be explained.

11. DATA ANALYSIS

A complete statistical analysis plan (SAP) will be written before the database lock.

11.1. SAMPLE SIZE

The primary objective of the study is to show that the combination of IV vinflunine and methotrexate is superior to methotrexate alone in terms of overall survival. Patients will be randomised in a 1:1 ratio.

The final analysis required at least 437 deaths to detect a statistically significant difference in the median OS of 7.5 months in the test arm versus 5.5 months in the control arm. This number of events gives a 90% power to show a difference between the two treatment arms using a two-sided log-rank test at an alpha = 0.05 significance level. An expected total number of 530 randomised patients was planned.

Following the sponsor's decision to stop the accrual, 459 patients have been randomised. The statistical analysis will be conducted on these 459 patients.

325 events are expected to observe at the end of study allowing a power of 80%.

Whatever the number of events at the end of study, the final analysis of OS (primary analysis) will be performed on the ITT population.

11.2. PROTOCOL DEVIATIONS

No eligibility review will be performed. Eligibility population and evaluable population for tumor response will not be defined.

11.3. POPULATION ANALYSED

11.3.1. Intent-to-treat population (ITT)

All randomised patients will be included in the Intent-To-Treat (ITT) population. They will be analysed in the arm they were assigned by randomisation.

11.3.2. Eligible population

The eligible population is a subset of the ITT population. To be eligible a patient should not have any major protocol deviations from inclusion and exclusion criteria. The major protocol deviations will be described in the SAP. The eligible patients will be analysed in the arm they were assigned by randomisation.

11.3.3. Evaluable population for tumour response

The evaluable population for tumour response is a subset of the Eligible population. To be included in the evaluable population, the patients have to be eligible, evaluable and treated in the arm assigned by randomisation.

To be evaluable a patient must satisfy the following conditions:

- Patients must have received a minimum of one study treatment administration and have tumour assessment at baseline and during study (after week 6) unless progression or death from progression is documented before the first on-study tumour assessment at week 6. In this case, the patient will be considered as evaluable with early progression,

– In patients with measurable disease, all baseline target lesions must have been assessed at least once 6 weeks after randomisation, with the same method of measurement as baseline,

– In patients with only non-measurable disease, non-target lesions must have been assessed at least once 6 weeks after randomisation, with the same method of measurement as baseline.

11.3.4. 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.

11.3.5. Evaluable population for health-related quality of life assessment

To be evaluable for health-related quality of life assessment, patients should have completed one questionnaire (at least two third of the questions) within seven days prior to randomisation, and at least one questionnaire (at least two third of the questions) during the study period. To be considered evaluable, the questionnaires should be available in the native language of the patient, otherwise, the patient will not be evaluable for quality of life.

11.4. DEFINITIONS

- Survival time

Survival time is measured from the date of randomisation up to death or last follow-up. For patients who have not died, survival duration will be censored at the date of last contact if the patient is lost to follow-up or at the date of last news.

- Objective Response Rate

The Objective Response Rate (ORR) will be calculated as follows:

$$ORR = \frac{\sum(\#CR + \#PR)}{N}$$

with:

- # CR = number of patients whose best response is CR,
- # PR = number of patients whose best response is PR,
- N = number of patients qualified for efficacy analysis.

- Disease Control Rate

The Disease Control Rate (DCR) will be calculated as follows:

$$DCR = \frac{\sum(\#CR+\#PR+\#SD)}{N}$$

with:

- # CR = number of patients whose best response is CR,
- # PR = number of patients whose best response is PR,
- # SD = number of patients whose best response is SD (SD does not include non CR/non PD),

- N = number of patients qualified for efficacy analysis.

Table 23: Definitions of ORR and DCR

Type of population analysed	Observed number of best responses
Measurable and/or non-measurable disease	CR PR **ORR =(CR + PR)/N** SD **DCR = (CR + PR + SD)/N** Non CR/Non PD* PD NE Total (N)
Measurable disease only	CR PR **ORR = (CR + PR)/N** SD **DCR = (CR + PR + SD)/N** PD NE Total (N)

* For patients with only non measurable disease

- Duration of objective response

The duration of objective response will be measured for responders (confirmed CR + PR) from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) later confirmed, until the date of progression or the date of death due to any cause. Patients who are lost to follow-up or reach the time point of analysis without a known record of progression or death will have the duration of response censored at the date of last tumour assessment or last contact date of a follow-up showing no progression, whichever occurred last. For patients who receive a new anti-cancer treatment in the absence of progression, the duration of response will be censored at the date of first administration of the new anti-cancer treatment.

- Duration of disease control

The duration of disease control will be measured for patients with objective response or stable disease, from the date of randomisation until the date of progression or the date of death whatever the cause. Patients who are lost to follow-up or reach the time point of analysis without a known record of progression or death will have the duration of disease control censored at the date of last tumour assessment or last contact date of a follow-up showing no progression, whichever occurred last. For patients who received a new anti-cancer treatment in the absence of progression, the duration of disease control will be censored at the date of first administration of this new anti-cancer treatment.

- Progression-free survival

Progression-free survival will be calculated from the date of randomisation until the date of progression or death (whatever the reason of death). Patients lost to follow-up, or without a known record of progression or death at time of analysis will have the progression-free survival censored at the date of last tumour assessment or the date of last contact of a follow-up showing no progression, whichever occurs last.

- Time to treatment failure

Time-to-treatment failure will be calculated from the date of randomisation up to the date of failure (progression, relapse, death or withdrawal due to adverse event, patient's refusal to continue, lost to follow-up or start of new anti-cancer therapy). Patients who reach the time point of analysis without failure as defined above will have the time to treatment failure censored at the date of last tumour assessment or last contact of a follow-up not showing progression. Patients who discontinued treatment for other reason and who are lost to follow-up will be censored at the date of last contact.

- Time to response

Time to response will be calculated from the date of randomisation up to the first report of documented response.

11.5. CLINICAL STATISTICAL METHODS

11.5.1. Statistical methodology

The statistical analysis will be performed by Institut de Recherche Pierre Fabre. Data will be analysed using the SAS® system software version 8.2 (or later if available) for Windows®. All statistical tests will be two-sided at a 5% level of significance unless otherwise specified.

Summary tables will be provided according to the standard format of Institut de Recherche Pierre Fabre developed for the vinflunine chemotherapy.

Continuous data will be summarized with the following items: frequency, median, (if n≥ 3), range and mean and standard error if relevant.

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

Whatever the number of events at the end of study, the final analysis of OS (primary analysis) will be performed on ITT population.

Only descriptive analyses will be performed on all secondary efficacy analyses for ITT population (secondary analyses on primary and secondary parameters, subgroup analyses, QoL).

Safety analyses will be performed as planned.

11.5.1.1. Statistical methods for categorical, ordinal and quantitative variables

11.5.1.1.1. 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.

11.5.1.1.2. 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.

11.5.1.1.3. 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 two 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.

11.5.1.2. Statistical methods for time to event 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 center) used at the time of randomisation.

Multivariate analyses will be performed to take account of prognostic factors. A stratified Cox proportional hazards model and a logistic regression will be applied to the Overall Survival, Progression-Free Survival, and tumour response, respectively. A stepwise procedure, with p = 8% to enter variables in the model and p = 10% to remove variables from the model, will be used to select the best model.

11.5.1.3. Statistical methods for health-related Quality of Life data

Repeated measures data will be analysed with a mixed effect model with change from baseline as the response. The most suitable covariance structure will be chosen according to Akaike's Information Criterion and Schwartz' Bayesian Criterion, between unstructured, compound symmetric and autoregressive of order 1.

11.5.2. Baseline assessment

All baseline data will be tabulated on the intent to treat population:

- Demographic data,
- Characteristics of the disease at diagnosis,
- Prior anti-cancer treatment,
- Clinical and biological parameters

11.5.3. Efficacy assessment

11.5.3.1. Efficacy parameters

11.5.3.1.1. Primary efficacy parameter

The primary efficacy parameter is overall survival.

11.5.3.1.2. Secondary efficacy parameters

The secondary efficacy parameters are:

- The Progression-Free survival in both arms,

- The Objective Response and Disease Control rates in both arms,
- The duration of response, disease control and time to first response in both arms.

11.5.3.2. Efficacy analyses

11.5.3.2.1. Primary efficacy analysis

The primary efficacy analysis will be led on the Overall Survival. The hypothesis of superiority will be accepted if the p-value from a stratified log-rank test is smaller than 0.05.

The stratification factors will be those used at the time of randomisation except center because of the high number of participating centers in the study :

- WHO performance status (0 versus 1),
- Refractory or resistant to platinum versus other,
- Prior radiotherapy (yes versus no),
- Prior treatment with anti-EGFR medication (yes versus no).

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

11.5.3.2.2. Supportive analysis of the primary efficacy parameter

To ensure the consistency of the primary endpoint, an additional OS analysis will be conducted on the Eligible population. A stratified log-rank test will be used to compare the two treatment arms. The stratification factors will be those defined above (see §11.5.3.2.1).

11.5.3.2.3. Sensitivity analyses of the primary parameter

In order to determine the role of the study treatments on survival, a sensitivity analysis will be done. In this analysis, the overall survival time will be censored at the time of the first further chemotherapy. As for the primary efficacy analysis, a stratified log-rank test will be used to compare the two treatment arms. The stratification factors will be those defined above (see §11.5.3.2.1). This analysis will be done on the ITT and Eligible population.

11.5.3.2.4. Secondary efficacy analyses

11.5.3.2.4.1. Overall survival

A multivariate analysis using a stratified Cox proportional hazard model for overall survival will be performed on the ITT and Eligible population. The stratification factors will be those defined above (see §11.5.3.2.1). The following prognostic factors will be taken into account :

- Age (< 50 years versus ≥ 50 years),
- Primary tumour site (oral cavity, oropharynx, larynx, hypopharynx, nasal cavity, other),
- Extent of disease (locoregional recurrence versus metastatic disease with or without locoregional recurrence,
- Tumour grade (well or moderately differentiated, poorly differentiated).

In case of missing data in some covariates of the multivariate analysis, in addition of the complete case analysis (listwise selection approach) consisting in omit those cases with missing data and to run the analysis on what remains, a multiple imputation based approach where complete data sets are drawn will be used to perform the multivariate analysis. The imputation model will be defined in the SAP.

11.5.3.2.4.2. Progression-Free Survival

The analysis of Progression-Free Survival (PFS) will be conducted on the ITT population and on the eligible population. A stratified log-rank test will be used to compare the two treatment arms. The stratification factors will be those defined above (see §11.5.3.2.1). In addition, the time interval between tumour assessments will be compared between the two arms. Median and range of time elapsed between two consecutive evaluations will be provided in both arms, overall and by cycle number.

Sensitivity analyses of PFS will be performed in the ITT population and in the eligible population. Firstly, an analysis will be conducted in which patients who did not show evidence of PD before starting new anti cancer therapy will be censored at the date of initiation of new anti-cancer therapy. Secondly, the analysis will be repeated considering the start of new anti-cancer therapy as

an event. These two analyses aim at ruling out the bias that could arrive from the potential imbalance of further anti-cancer therapy between the two arms.

Another sensitive analysis will consider the patient in progression the day after the last tumor assessment showing no progression. For patients who progressed early or were assessed as PD at the first evaluation, they will be considered as progressing at the day after the date of randomisation. This analysis aims at ruling out potential ascertainment bias and taking into account the potential imbalance of early progressors between the two treatment arms.

A multivariate analysis using a stratified Cox proportional hazard model for Progression-Free Survival will be performed on the ITT and Eligible population with the same stratification factors as described above (see §11.5.3.2.1). The following prognostic factors will be taken into account :

- Age (< 50 years versus ≥ 50 years),
- Primary tumour site (oral cavity, oropharynx, larynx, hypopharynx, nasal cavity, other),
- Extent of disease (locoregional recurrence versus metastatic disease with or without locoregional recurrence,
- Tumour grade (well or moderately differentiated, poorly differentiated).

In case of missing data in some covariates of the multivariate analysis, in addition of the complete case analysis (listwise selection approach) consisting in omit those cases with missing data and to run the analysis on what remains, a multiple imputation based approach where complete data sets are drawn will be used to perform the multivariate analysis. The imputation model will be defined in the SAP.

11.5.3.2.4.3. Tumour response

The analyses of tumour response will be performed on the ITT population and on the population evaluable for response in the two treatment arms.

- ❖ Objective Response and Disease Control Rate

Objective Response Rate and Disease Control Rate in each treatment arm will be estimated and presented along with a corresponding 95% confidence interval. The ORR and DCR will be

compared between the two arms with a Cochran-Mantel-Haenszel (CMH) test. The stratification factors will be those defined above (see §11.5.3.2.1).

Furthermore, the ORR and DCR will be estimated and compared between the two treatment arms in the subgroups of patients entering the study with measurable disease (i.e. excluding patients with only non-target lesions at baseline).

A logistic regression for ORR and DCR will be performed in order to take into account the following prognostic factors:

- WHO performance status (0 versus 1),
- Refractory or resistant to platinum versus other,
- Prior radiotherapy (yes versus no),
- Prior treatment with anti-EGFR medication (yes versus no),
- Age (< 50 years versus ≥ 50 years),
- Primary tumour site (oral cavity, oropharynx, larynx, hypopharynx, nasal cavity, other),
- Extent of disease (locoregional recurrence versus metastatic disease with or without locoregional recurrence,
- Tumour grade (well or moderately differentiated, poorly differentiated).

❖ Time to first response

The time to first response will be described in the ITT population and the evaluable population for response. No formal statistical comparisons are planned.

❖ Duration of response and disease control

Duration of response and duration of disease control will be analysed on the ITT and evaluable for response populations. A stratified log-rank test will be used to compare the two treatment arms. The stratification factors will be those defined above (see §11.5.3.2.1).

Both analyses of duration of response and duration of disease control will be repeated in patients with measurable disease at study entry (i.e. excluding patients with only non-target lesions at baseline).

11.5.3.2.4.4. Subgroups analyses

Descriptive subgroup analyses of Overall Survival, Progression-Free Survival, DCR and ORR will be performed according to:

- WHO performance status (0 versus 1),
- Refractory or resistant to platinum versus other,
- Prior radiotherapy (yes versus no),
- Prior treatment with anti-EGFR medication (yes versus no),
- Age (< 50 years versus ≥ 50 years),
- Primary tumour site (oral cavity, oropharynx, larynx, hypopharynx, nasal cavity, other),
- Extent of disease (locoregional recurrence versus metastatic disease with or without locoregional recurrence,
- Tumour grade (well or moderately differentiated, poorly differentiated).

These analyses will be conducted on the ITT and Eligible populations for Overall Survival and Progression-Free Survival, and on the ITT and evaluable for response populations for DCR and ORR. No formal statistical comparisons are planned.

11.5.4. Safety assessment

11.5.4.1. Safety parameters

Haematological parameters (WBC, ANC, platelets, haemoglobin), febrile neutropenia, biochemical parameters (ALT, AST, alkaline phosphatase, creatinine, total bilirubin) and non haematological toxicities will be assessed. The NCI CTC AE version 3.0 will be used.

11.5.4.2. Safety analyses

The safety analysis will be performed in the evaluable population for safety. For haematological and biochemical parameters, the worst NCI CTCAE version 3.0 grade will be presented by patient and by cycle. The maximum NCI CTC AE version 3.0 grade or severity will be reported by patient for each treatment-emergent adverse event. All analyses will be performed in two different ways: regardless of relationship to study treatment and related to study treatment.

The analyses will present the NCI CTC AE version 3.0 grades tabulated for each MedDRA "System Organ Class" (SOC) and "Preferred Term" (PT) per patient.

In order to analyse the evolution of the biochemical toxicities, the worst NCI CTC AE version 3.0 grade will be analysed according to the grade present at baseline.

In addition, the relationship between the presence of liver metastases at baseline and the worst NCI CTC AE version 3.0 grade during study will be studied for AST, ALT and bilirubin. The same analysis will be done for the worst NCI CTC AE version 3.0 grade of alkaline phosphatase and the presence of liver and/or bone metastases at baseline.

The number of all serious adverse events and related serious adverse events will be tabulated by treatment arm. Serious adverse events will be reported by patient.

11.5.5. Quality of life assessment

Change in disease related symptoms will be assessed using the EORTC QLQ-C30 questionnaire and the QLQ-Head and Neck 35 EORTC module.

11.5.5.1. Health-related quality of life parameters

Health-related quality of life parameters will be the fifteen scales that can be derived from the 30 questions of the EORTC QLQ-C30 questionnaire:

- A global health-related quality of life scale,
- Five functional scales: physical, role, cognitive, emotional, social,
- Nine symptom scales: nausea and vomiting, pain, fatigue, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties.

The QLQ-H&N 35 EORTC module will also be used to assess health-related quality of life. Eighteen scales are derived from the 35 questions of the QLQ-H&N 35 EORTC module :

- Seven multi-item scales that assessed Pain, Swallowing, Senses, Speech, Social eating, Social contact and Sexuality.

- Eleven single item : Teeth, Opening mouth, Dry mouth, Sticky saliva, Coughing, Feeling ill, Use of pain killers, Use of nutritional supplement, Use of feeding tube, Lost of weight and Gain of weight.

11.5.5.2. Health-related quality of life analyses

The analysis of health-related quality of life will be done on the evaluable population for quality of life. Compliance with the questionnaires will be displayed per evaluation. Compliance is defined as the number of forms actually received as a proportion of those expected. The number of QoL questionnaires completed and evaluable per evaluation will also be given. The number of patients non evaluable for health-related quality of life analysis and reasons for non-evaluability will be tabulated.

Each parameter will be described at baseline. Changes of the scores from baseline of the parameters (15 for QLQ-C30 and 13 for QLQ-H&N 35) will be provided. Figures will be displayed in order to show the evolution of each scale.

A repeated measure analysis will be performed for all scales and single items with change from baseline as the response.

11.5.6. Interim analyses

An Independent Data Monitoring Committee (IDMC) will be set up to ensure that for patients participating in the study there is no increased risk for harm. This IDMC will review study data as detailed below. The analyses will be performed by an internal statistician independent from the study. A separate IDMC charter will describe the activities of this committee.

11.5.6.1. Early Safety Review

An early safety review of data will be done by the IDMC after 40 patients are randomised (20 in each arm) and treated for at least 1 cycle.

11.5.6.2. Efficacy and Safety Interim Analysis

An interim analysis based on the non progression rate at 6 weeks will be performed after tumour response data from the first 100 randomised patients in the test arm become available. The main purpose of this interim analysis is to stop the study if result indicating poor efficacy of the test regimen is observed. It is assumed that the test arm will be of no further interest in the second-line treatment of SCCHN patients if the observed non-progression rate at 6 weeks (first tumour assessment scheduled) is less than the lower limit of the 95% CI of the expected non-progression rate at 6 weeks. Assuming that this expected non-progression rate at 6 weeks is equal to 61%, the 95% CI is [51%-71%] and the study will be stopped prematurely if $\geq$ 49 progressions (or deaths for progression) out of 100 evaluable patients for efficacy will be observed.

To be evaluable a patient must satisfy the following conditions:

- Patients must have received a minimum of one study treatment administration and have tumour assessment at baseline and during study (after week 6) unless progression or death from progression is documented before the first on-study tumour assessment at week 6. In this case, the patient will be considered as evaluable with early progression,
- In patients with measurable disease, all baseline target lesions must have been assessed at least once 6 weeks after randomisation, with the same method of measurement as baseline,
- In patients with only non-measurable disease, non-target lesions must have been assessed at least once 6 weeks after randomisation, with the same method of measurement as baseline.

No formal early stopping rule on safety criteria will be applied. However, given the toxicity associated with IV vinflunine and methotrexate a special attention will be paid to the rates of :

- febrile neutropenia
- neutropenic infection
- grade 3-4 ileus
- and toxic deaths

The results of the interim analysis will be submitted to IDMC for their recommendation to pursue or stop accrual in the study.

Tumour responses will be collected as soon as patients have been evaluated by the investigators. Adverse events reporting will be also closely monitored. Because the projected patient accrual could be slow in the study, the patient enrolment will continue while waiting the decision of the IDMC.

Following this interim analysis, a futility analysis has been carried out.

The results of this analysis showed that the probability to demonstrate a significant benefit of overall survival at the time of the final analysis is very low.

As a consequence, the sponsor has decided to stop the recruitment of study patients on 16th October 2015.

12. STUDY MONITORING AND DATA COLLECTION

12.1. DATA COLLECTION

12.1.1. CRF / eCRF

All data obtained in the study described in this protocol will be recorded on CRFs. The CRF for each subject will be presented in a paper or electronic folder. The CRF / eCRF will be completed chronologically and updated regularly in order to reflect the most recent data on the patient included in the study.

Prior to the start of the study, the Investigator will complete a "Delegation of significant study related duties" form, showing the signatures and initials of all those who are authorised to make or change entries on the CRFs / eCRFs.

In case of paper CRF, it must be neatly filled in with a black-inked pen. For each page on which information is entered, the subject number must be recorded. The Registration form, end of treatment form and the follow-up status form(s) must be dated and signed by an authorised

Investigator. Errors must be corrected by drawing a single line through the incorrect entry and by writing the new value as close as possible to the original. The correction must then be initialled and dated by an authorised person.

Although subjects may be interviewed by a research nurse or the trained equivalent (*e.g.* medical student, physician's assistant), the Investigator must verify that all data entries are accurate and correct, including verification that the subject fulfils the criteria for entrance into the study before study medication is dispensed. Physical examinations have to be performed by a registered medical practitioner.

The End of Treatment Form must be completed for each patient either finishing the study or dropping out from it.

In case of paper CRF, original forms (or top pages of forms) and the first 2 copies of these forms are retrieved by the Sponsor. The fourth copies are retained in investigator files.

In case of eCRF, data will be transmitted securely on a server.

The data may have to be used to support efficacy and/or safety claims, and therefore may have to be submitted for inspection to Health Authorities. If the Investigator moves, the subject files will be kept in the hospital archives.

12.1.2. Source documents

Definition:

- Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

- Source Documents: Original documents, data, and records (*e.g.* hospital records, clinical and office charts, laboratory notes, memoranda, records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies,

microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

The patients must have consented to allow their medical records to be viewed by sponsor-authorised personnel and by regulatory authorities. This information is included in the informed consent.

12.2. STUDY MONITORING

Before selecting an investigational centre for the study, a pre-selection visit will be performed to verify that the site, the equipment and the staff comply with the protocol requirements and GCP guidelines.

A Clinical Research Associate (CRA) will be appointed by the Institut de Recherche Pierre Fabre to monitor this study and periodically contact the site, including conducting on site visits.

CRA activities will include:

- Site initiation visit to collect and distribute essential pre-study documents ; to instruct the investigator and site personnel about the protocol, study procedures and expectations; to obtain investigator's assurance to comply with study requirements and GCP guidelines and to inform the investigator and appropriate study staff about study materials.

- Monitoring visits : according to Good Clinical Practices, the study CRAs involved in the present study are fully instructed concerning confidentiality and able to perform any necessary control on informed consent and CRFs / eCRFs, including cross-checking clinical and laboratory data with the patient's file. All observations and findings should be verifiable. During monitoring visits, Institut de Recherche Pierre Fabre CRA will:

  - check and assess the progress of the study,
  - review collected study data,
  - conduct Source Document Verification (hospital files),

- identify any issue and address its resolution.

This will be done in order to verify that the:

- data are authentic, accurate, and complete,
- safety and rights of subjects are being protected,
- study is conducted in accordance with the currently approved protocol (and any amendments), GCP and all applicable regulatory requirements.

The investigator agrees to allow the CRA direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the CRA to discuss findings and any relevant issues.

- Termination visit: at study closure. CRAs will also conduct all activities as indicated in section 15.3.

13. DATA MANAGEMENT

13.1. DATA ENTRY

The study data will be entered into a database in an ongoing basis. In case of paper CRF, independent double data entry will be performed by two different trained operators. The two entries will be compared in order to identify and resolve any data entry errors.

13.2. DATA REVIEW

Consistency checks will be performed on the data. The resulting edit queries will be transmitted to the monitoring team. Answers to these queries endorsed by the investigator will be integrated into the database.

13.3. DATA CODING

Adverse events will be graded according to the NCI CTCAE version 3.0 scale.

Adverse events will be coded according to MedDRA Dictionary.

Concomitant medications will be coded according to WHO drug Dictionary.

13.4. DATA STORAGE

Data will be entered in databases and stored in a secure area on a server.

13.5. DATA FREEZING

After corrections and modifications have been performed, the databases will be locked.

The data will be extracted from the databases into the SAS data files for statistical analysis.

14. GENERAL ETHICAL CONSIDERATIONS

14.1. ETHICAL CONDITIONS

This study will be performed in accordance with the principles stated in the Declaration of Helsinki and subsequent amendments (Appendix 1) and in accordance with the Good Clinical Practice Guideline (CPMP/ICH/135/95).

14.2. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

All the documents required by National Regulations and any other informative documents that may be requested will be submitted for review to an Ethics Committee whose procedures and operations meet the National Legal Requirements.

Depending on National Regulations, the application is submitted to the EC by the sponsor or by the investigator.

A copy of the formal written approval from the EC is provided to the sponsor (directly by the EC or via the investigator) with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or notification (depending on National Regulations) is carried out by the sponsor.

The screening of subjects does not start before the approval of the EC has been obtained and the study authorised by the Competent Authority (or notified to the Competent Authority, depending on the National Regulations).

14.3. SUBJECT'S INFORMATION LEAFLET, CONSENT FORM AND SUBJECT CARD

14.3.1. Subject's information leaflet and consent form

Any information must be given to the subjects before their decision to participate or abstain from participation.

This information is based on the elements set out in the Declaration of Helsinki and the ICH GCP Guideline. It must also describe the measures taken to safeguard subject's privacy and protection of personal data, according to European Directive 95/46 EC.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the investigator and/or their future care.

The written information and consent form must be submitted to the subject with an oral explanation. It must be agreed and signed by the subject before any study-related procedure starts.

<u>This information and consent procedure is under the investigator's responsibility.</u>

The information and consent document are made in triplicate: the original copy is kept by the investigator, one copy is given to the subject and the last copy is kept by the Clinical Quality Assurance Unit of the sponsor in a sealed envelope at the end of study.

Specific areas of the sponsor's copy are not triplicated to avoid the reading of the subject's surname first name, address and signature.

If any information becomes available during the trial that may be relevant to the subject's willingness to keep on participating in the trial, an updated written informed consent must be submitted to the subject to confirm his agreement to continue participating.

14.3.2. Subject card

The patient will receive from the Investigating Centre a personal card to be kept all along the study duration and providing the following information: Patient's name, Sponsor's name, study code, EUDRACT number, date of treatment start, complete address of the Investigating Centre with the name and phone number of the Investigator and a sponsor 24H/24 phone contact number (French and English languages) : 33 (0) 5 63 35 25 83.

14.4. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) are entered into a computer under the sponsor's responsibility in accordance with the French law, "Loi informatique et Libertés" (January 6, 1978 and subsequent amendments) and with the European Directive 95/46/EC.

14.5. INSURANCE POLICY

In accordance with the provisions of the law and ICH GCP, PFM has an insurance policy intended to guarantee against possible damages resulting from research.

The studies and/or experiments performed on behalf of PFM are specifically and expressly guaranteed. It is advisable to underline that non compliance with the research legal conditions are clauses of guarantee exclusion.

15. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the investigator nor the sponsor may alter the protocol without the permission of the other parties.

All changes to the protocol will be subject to an amendment which must be dated and signed by both parties and must appear as an addendum to the protocol.

Substantial amendments are submitted for approval/authorization to Ethics Committee and Competent Authorities. Urgent amendments are submitted for approval/authorization to Ethics Committee and Competent Authorities but could be implemented immediately under specific conditions defined with the sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATORS FILE STORAGE

The investigator:

- keeps all trial-related documents in appropriate file folders. Records of subjects, original informed consent forms, source documents, case report forms, drug inventory, EC and sponsor correspondence pertaining to the study must be kept on file;
- retains all documents relating to the screening (consent and investigation results) of all subjects included in the trial or not;
- retains a list of the subjects names, addresses (and/or number of medical file), code numbers, dates of entry into and completion of the trial period, to allow checking of data reported on CRFs / eCRFs with those from source documents;
- authorises direct access to source documents for monitoring, audits and inspections.

The trial-related documents must be retained as strictly confidential at the investigator's site for at least 15 years after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF STUDY

15.3.1. End of study

The end of the study is the date of the last patient study treatment administration plus 30 days.

Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early study termination

15.3.2.1. Early study termination decided by the sponsor

The sponsor may discontinue the study at any time for any of the following reasons:

- Emerging adverse events of such a serious nature that continuation of the study becomes unacceptable;
- Decision to stop the study based on the results of the interim analysis;
- Recruitment rate too low to expect completion of the study in its present form within the period foreseen for inclusions;
- Deviations from Good Clinical Practice and/or regulations;
- Decision to stop drug development.

If the study is prematurely discontinued, all study data must be returned to IRPF. In addition, the site must conduct final disposition of all unused study drugs in accordance with IRPF procedures for the study.

15.3.2.2. Early study termination decided by the Competent Authorities

The Competent Authorities may suspend or prohibit a study if it considers that the conditions of authorisation are not being met or has doubt about the safety or scientific validity of the study.

15.4. AUDIT

The sponsor is responsible for making sure that both his representatives (monitor, clinical research assistant) and the investigator fulfil their requirements as specified by the GCP guidelines. The audit can be made internally at IRPF and at the investigational site where the CRFs / eCRFs are matched against source documents. Possibility to have a direct access to all study documentation is

compulsory. The practical conditions for the audit will be discussed between the investigator and the Clinical Quality Assurance Department.

Oral information about the audit results will be given to the investigator.

15.5. INSPECTION

The Health Care Authorities may inspect any investigation site or the sponsor during the course of the study or following its completion, to verify the conduct of the study and quality of the data. The investigator will provide direct access to source documents.

15.6. CONFIDENTIALITY

The present materials (protocol, CRF, investigator's brochure) contain confidential information.

Except if agreed to in writing with the monitor, the investigators must hold such information confidential, and must not disclose it to others (except where required by applicable law).

15.7. CLINICAL STUDY REPORT

Data analysis, statistical reporting and clinical research report preparation will be the responsibility of the sponsor or its designee. Upon completion of the data analysis, a final report, including a review of the objectives and methods, a presentation and discussion of the results will be drawn up according to ICH Guidelines (Structure and Content of Clinical Study Reports, ICH-E3, CPMP/ICH/137/95). This report will be a clinical and statistical integrated report. This report will be signed by the sponsor representatives and the coordinating investigators.

15.8. STUDY RESULTS COMMUNICATION

Upon completion of the study, global results of the Research will be communicated to the investigator. According to the Local Regulations, the patient can ask the investigator for the results (only if applicable in the concerned country).

15.9. PUBLICATIONS

The information and data collected during the conduct of this clinical study are considered confidential and will be used by the sponsor in connection with the development of the study drug. These information may be disclosed as seemed necessary by the sponsor.

To allow for use of information derived from this clinical study and to insure compliance with current regulations, the investigator is obliged to provide the sponsor with complete test results and all data developed in this study. Only the sponsor may make information obtained during this study available to the physicians and to regulatory agencies, except as required by regulation.

All the results of this study including data reports, discoveries and inventions resulting from the study, are the property of the sponsor.

In the event the sponsor chooses to publish the data from this study, the sponsor may provide the author(s) of the study with a manuscript at least 30 days prior to the expected date of submission to the intended publisher.

The investigators reserve the right to publish or present the results of this study provided that a copy of the manuscript or abstract is made available to Institut de Recherche Pierre Fabre for review at least 30 days prior to the expected date of submission to the intended publisher or planned presentation.

In addition, if necessary, investigators shall withhold publication an additional 60 days to allow the filing of a patent application or to allow the sponsor to take any measures he deems appropriate to establish and preserve his proprietary rights.

It is agreed that publication of the results of the study by each site shall be made only as part of a publication of the results of the study obtained by all sites performing the protocol, once the study is completed and finalised. This publication will be the responsibility of the sponsor and the investigators.

The names on the author list will be given according to the participation in the design of the protocol as well as taking into consideration the accrual of eligible and evaluable patients by the investigators in each centre.

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Appendix 1: World medical association declaration of Helsinki

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words,

"The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by

individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and

standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain

for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made

publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix 2: Performance status scale

PERFORMANCE STATUS SCALE
KARNOFSKY AND W.H.O CLASSIFICATION

KARNOFSKY (%)		WHO PS	
100	Normal, no complaints, no evidence of disease	0	Able to carry out all normal activity without restriction
90	Able to carry on normal activity, minor signs or symptoms of disease		
80	Normal activity with effort, some signs or symptoms of disease	1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
70	Cares for self, unable to carry on normal activity or to do active works.		
60	Requires occasional assistance but is able to care for most needs.	2	Ambulatory and capable of all self-care but unable to carry out any work ; up about more than 50% of waking hours.
50	Requires considerable assistance and frequent medical care.		
40	Disabled, requires special care and assistance	3	Capable of only limited self-care ; confined to bed or chair more than 50 % of waking hours.
30	Severely disabled, hospitalisation is indicated although death not imminent		
20	Very sick, hospitalisation necessary, active supportive treatment necessary	4	Completely disabled ; cannot carry out any self-care ; totally confined to bed or chair.
10	Moribund, fatal processes progressing rapidly		
0	Dead	5	Dead

Appendix 3: Distribution of active bone marrow in the adult

DISTRIBUTION OF ACTIVE BONE MARROW IN THE ADULT[a]

Site	Percent of Total[b]
Cranium and mandible	13
Humeri, Scapulae, Clavicles	8
Sternum and Ribs	10
Vertebrae	28
Pelvic bones	34
Femur	4

a. Adpated from Ellis RE, the distribution of active bone marrow in the adult. Phys Med Bio. 5:255, 1960-1961.

b. Percentage represents total radiation of site(s).

PERCENT OF NORMAL BONE MARROW IRRADIATED USING STANDARD RADIATION PORTS*

	Marrow volume at risk
Skull (not including mandible)	12 %
Upper limb girdle (unilateral) (humeral head, scapulae, clavicle)	4 %
Sternum	2 %
Ribs (all)	8 %
Ribs (hemithorax)	4 %
Cervical vertebrae (all)	3 %
Thoracic vertebrae (all)	14 %
Lumbar vertebrae (all)	11 %
Sacrum	14 %
Pelvis (including both innominates and both femoral heads and necks)	26 %
Mantle (approximate)	25 %
Upper para aortic nodes (approximate)	11 %
Inverted Y (approximate)	45 %

Appendix 4: Treatment labelling

LABELLING OF VIAL OF VINFLUNINE 50MG – 2ML

GREEN TEAR-OFF LABEL FOR DRUG ACCOUNTABILITY FORM

PIERRE FABRE MEDICAMENT

L00070 IN 309 F0

L0070IN

50 mg - 2 mL (25 mg /mL)

PC201XXXXX - XXXX** - # YYYYY* - EXP MM/YYYY

** : TREATMENT NUMBER - * : BATCH NUMBER

GREEN FIXED LABEL

PIERRE FABRE MEDICAMENT
45, Place Abel Gance - 92100 Boulogne - France

L00070 IN 309 F0

L0070IN

50 mg - 2 mL (25 mg /mL)

INTRAVENOUS USE

PC201XXXXX - XXXX** - # YYYYY* - EXP MM/YYYY

** : TREATMENT NUMBER - * : BATCH NUMBER

LABELLING OF BOX OF VINFLUNINE 50MG – 2ML

On the first page of the booklet label, there will be the name, the address and the phone number of the sponsor and the EudraCT number. The other pages of the booklet label will bear the following information :

PROTOCOL L00070 IN 309 F0

PACKAGING BATCH N° ……
TREATMENT N° ……
EXPIRY DATE……..

SEE ON THE FIRST PAGE

BOX OF 10 SINGLE USE VIALS OF L0070IN VINFLUNINE (AS DITARTRATE)

50 mg - 2 mL
25 mg / mL
(vinflunine base)

CONCENTRATE FOR SOLUTION FOR INFUSION - INTRAVENOUS USE
TO BE DILUTED PRIOR TO ADMINISTRATION
FOLLOW THE PRESCRIBED DOSES AND THE STORAGE CONDITIONS AFTER RECONSTITUTION
STORE IN A REFRIGERATOR (+2°C/+8°C)
STORE IN THE ORIGINAL BOX IN ORDER TO PROTECT FROM LIGHT
STICK THE **GREEN** TEAR-OFF LABEL FROM THE USED VIALS ON THE PATIENT "DRUG ACCOUNTABILITY FORM"
FOR CLINICAL TRIAL USE ONLY

LABELLING OF VIAL OF VINFLUNINE 250MG – 10ML

WHITE TEAR-OFF LABEL FOR DRUG ACCOUNTABILITY FORM

PIERRE FABRE MEDICAMENT

L00070 IN 309 F0

L0070IN

250 mg - 10 mL (25 mg /mL)

PC201XXXXX - XXXX** - # YYYYY* - EXP MM/YYYY

** : TREATMENT NUMBER - * : BATCH NUMBER

WHITE FIXED LABEL

PIERRE FABRE MEDICAMENT
45, Place Abel Gance - 92100 Boulogne - France

L00070 IN 309 F0

L0070IN

250 mg - 10 mL (25 mg /mL)

INTRAVENOUS USE

PC201XXXXX - XXXX** - # YYYYY* - EXP MM/YYYY

** : TREATMENT NUMBER - * : BATCH NUMBER

LABELLING OF BOX OF VINFLUNINE 250MG – 10ML

On the first page of the booklet label, there will be the name, the address and the phone number of the sponsor and the EudraCT number. The other pages of the booklet label will bear the following information :

PROTOCOL L00070 IN 309 F0

PACKAGING BATCH N° ……
TREATMENT N° ……
EXPIRY DATE……..

SEE ON THE FIRST PAGE

BOX OF 10 SINGLE USE VIALS OF L0070IN VINFLUNINE (AS DITARTRATE)

250 mg - 10 mL
25 mg / mL
(vinflunine base)

CONCENTRATE FOR SOLUTION FOR INFUSION - INTRAVENOUS USE
TO BE DILUTED PRIOR TO ADMINISTRATION
FOLLOW THE PRESCRIBED DOSES AND THE STORAGE CONDITIONS AFTER RECONSTITUTION
STORE IN A REFRIGERATOR (+2°C/+8°C)
STORE IN THE ORIGINAL BOX IN ORDER TO PROTECT FROM LIGHT
STICK THE **WHITE** TEAR-OFF LABEL FROM THE USED VIALS ON THE PATIENT "DRUG ACCOUNTABILITY FORM"
FOR CLINICAL TRIAL USE ONLY

LABELLING OF THE VIAL OF METHOTREXATE 50MG

PIERRE FABRE MEDICAMENT 45, Place Abel Gance - 92100 Boulogne - France L00070 IN 309 F0 **METHOTREXATE** **50mg - 2mL (25mg/mL)** INTRAVENOUS USE PC201XXXXX - XXXX** - # YYYYY* EXP MM/YYYY	PIERRE FABRE MEDICAMENT L00070 IN 309 F0 METHOTREXATE 50mg - 2mL (25mg/mL) PC201XXXXX - XXXX** - # YYYYY* EXP MM/YYYY

** : Treatment number / * : Batch number

☐ : fixed label ⬚ : tear-off label

LABELLING OF THE BOX OF METHOTREXATE 50MG

On the first page of the booklet label, there will be the name, the address and the phone number of the sponsor, the EudraCT number. The other pages of the booklet label will bear the following information :

PROTOCOL L00070 IN 309 F0

PACKAGING BATCH N° ……
TREATMENT N° …… } SEE ON THE FIRST PAGE

BOX OF 10 VIALS OF METHOTREXATE MYLAN 50mg-2mL,
SOLUTION FOR INJECTION - INTRAVENOUS USE
FOLLOW THE PRESCRIBED DOSES
STORE BELOW 25°C
STORE IN THE ORIGINAL BOX IN ORDER TO PROTECT FROM LIGHT
TO BE ADMINISTERED WITHIN 12 HOURS AFTER DILUTION
STICK THE TEAR-OFF LABEL FROM THE USED VIAL ON THE PATIENT "DRUG ACCOUNTABILITY FORM"
FOR CLINICAL TRIAL USE ONLY

At the shipment, a label with the name of the investigator is sticked on each box of vinflunine 50mg, vinflunine 250mg and methotrexate 50mg.

Appendix 5: Serious adverse event report form

Pierre Fabre Médicament	DRUG :	Protocol N° :	Page 1/2
	Patient's Country ______	Patient No |__|__|__|__|__|__|	SAE No |__|__|

SERIOUS ADVERSE EVENT (SAE) NOTIFICATION FORM

TO BE TRANSMITTED TO THE CORPORATE VIGILANCES DIVISION
BY E-MAIL WITHIN 24H TO HQ.pharmacovigilance@pierre-fabre.com
OR BY FAX WITHIN 24H – FAX: 33 (0) 1.49.10.80.90

INITIAL ☐

FOLLOW UP ☐ No |__|

➢ SUBJECT DEMOGRAPHICS

Birth date : ___/___/___ Gender : |__| 1=M, 2=F Height : |__|__|__| cm Weight : |__|__|__|•|__| Kg

➢ DESCRIPTION OF THE EVENT(S)

Serious Adverse Event(s) (serious diagnosis / syndrome(s) or isolated serious sign(s)/symptoms) *(to be consistent with AE form)* please indicate NCI CTCAE v3.0 grade (1-5)	Seriousness 1 = Results in death (whatever might be the cause) 2= Life threatening 3= Involves inpatient hospitalisation** 4= Prolongs existing inpatient hospitalisation** 5= Results in persistent or significant disability or incapacity 6=Congenital anomaly or Birth defect 7=Other medically important condition*	**Onset Date (for seriousness)** *(dd/mm/yy)* & **Date Ceased (for seriousness)** *(dd/mm/yy)*	Outcome 1=recovered / resolved 2=recovering / resolving 3=not recovered / not resolved 4=recovered / resolved with sequelae 5=fatal 6=unknown	Action Taken with Study Medication 0=none 1=dose delayed 2=dose reduced 3=dose delayed and reduced 4= temporarily cancelled 5=infusion interrupted 6=permanently discontinued	Causality 1=Suspected 2=Not Suspected
Grade : |__|	|__| |__| |__|	Onset : ___/___/___ Ceased : ___/___/___ *Ongoing* : ☐	|__|	Study Drug 1 |__| Study Drug 2 |__|	Study Drug 1 |__| Study Drug 2 |__|
Grade : |__|	|__| |__| |__|	Onset : ___/___/___ Ceased : ___/___/___ *Ongoing* : ☐	|__|	Study Drug 1 |__| Study Drug 2 |__|	Study Drug 1 |__| Study Drug 2 |__|
Grade : |__|	|__| |__| |__|	Onset : ___/___/___ Ceased : ___/___/___ *Ongoing* : ☐	|__|	Study Drug 1 |__| Study Drug 2 |__|	Study Drug 1 |__| Study Drug 2 |__|
Grade : |__|	|__| |__| |__|	Onset : ___/___/___ Ceased : ___/___/___ *Ongoing* : ☐	|__|	Study Drug 1 |__| Study Drug 2 |__|	Study Drug 1 |__| Study Drug 2 |__|

Investigator's name : **Signature :** **Transmission Date :** ___/___/_____

* Other events such as cancer, and any additional adverse experience or abnormal laboratory values occurring during the study period, defined by the protocol as serious or which the investigator considers significant enough, or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events. Any overdosage meeting a seriousness criteria should be reported as a SAE. Any pregnancy occuring during / after exposure to the study drug(s) should be reported on the SAE notification form

** Except hospitalisations which duration and principle are planned by the protocol.

PSD.01.FOR.033_V5 May 2013

Pierre Fabre Médicament	DRUG :	Protocol N° :	Page 2/2
	Patient's Country _____	Patient No |__|__|__|__|__|__|	SAE No |__|__|

INITIAL REPORT ☐ **FOLLOW UP REPORT ☐** N° |__|

➢ **COMMENT SECTION**

Please comment the SAE (Summarize the chronology of the occurrence of the SAE, indicating the start date of event(s), specifying any significant medical history. Any additional relevant data ,investigational results, patient's hospital report will also be shortly documented (please attach a copy of the relevant documents).

SAE suspected to be due to protocol-related study procedures ? ☐ YES ☐ NO

Hospital discharge date : ___/___/____

In case of death: Date of death : ___/___/____

Has an autopsy been conducted ? ☐ YES ☐ NO If Yes, date of autopsy : ___/___/____ and available results:

➢ **STUDY DRUG(s)**

Drug Name	Dose (mg/m²)	Total dose (mg)	Route of admin.	Dates of administration & Cycle *(dd/mm/yy)*
First Administration				
Study drug 1	_____	_____	_____	___/___/____
Study drug 2	_____	_____	_____	___/___/____
Last Administration before SAE				
Study drug 1	_____	_____	_____	___/___/____ Cycle No : |__|__|
Study drug 2	_____	_____	_____	___/___/____ Cycle No : |__|__|

➢ **CONCOMITANT MEDICATIONS FROM TRIAL INITIATION TO THE OCCURRENCE OF THE SAE**

Trade Name (or INN)	Route of admin.	Daily dose	Start date *(dd/mm/yy)*	Stop date *(dd/mm/yy)*	Ongoing at occurrence of the event	Indication
			___/___/____	___/___/____	☐	
			___/___/____	___/___/____	☐	
			___/___/____	___/___/____	☐	
			___/___/____	___/___/____	☐	

➢ **CORRECTIVE MEDICATIONS TO TREAT THE SAE**

Trade Name (or INN)	Route of admin.	Daily dose	Start date *(dd/mm/yy)*	Stop date *(dd/mm/yy)*	Ongoing	Indication
			___/___/____	___/___/____	☐	
			___/___/____	___/___/____	☐	
			___/___/____	___/___/____	☐	

Investigator's name : **Signature :**

PSD.01.FOR.033_V5 May 2013

Appendix 6: Drug accountability form

☐ **Original: monitor**
☐ **1st copy: investigator/pharmacist**

Drug : **VINFLUNINE**	Protocol No : **L00070 IN 309 F0**	Page 1 / 1
Subject No |__|__|__|__|__|__|	**Subject's Drug Accountability Form**	

A PHASE III TRIAL OF IV VINFLUNINE IN COMBINATION WITH METHOTREXATE VERSUS METHOTREXATE ALONE IN PATIENTS WITH RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK PREVIOUSLY TREATED WITH PLATINUM-BASED THERAPY

ARM A

CYCLE N° : |__|__| **DATE OF DISPENSATION :** |__|__| |__|__| |__|__|__|__|

- **VINFLUNINE**

Dispenser's Initials	Dose level (mg/m²)	Dose dispensed (mg)	Number of vials 50 mg / 2 mL	Number of vials 250 mg / 10 mL	Date control CRA
	|__|__|__|	|__|__|__|	|__|__|	|__|__|	

When possible, please use the vials **in chronological order** and stick here the labels.

*Comments :*_____

_____

Date : |__|__| |__|__| |__|__|__|__|

INVESTIGATOR/PHARMACIST:

Name : _____ ***Signature :***

C.R.A.:

Name : _____ ***Signature :***

☐ **Original: monitor**
☐ **1st copy: investigator/pharmacist**

Drug : **VINFLUNINE**	Protocol No : **L00070 IN 309 F0**	Page 1 / 1
Subject No |__|__|__|__|__|__|	**Subject's Drug Accountability Form**	

A PHASE III TRIAL OF IV VINFLUNINE IN COMBINATION WITH METHOTREXATE VERSUS METHOTREXATE ALONE IN PATIENTS WITH RECURRENT OR METASTATIC SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK PREVIOUSLY TREATED WITH PLATINUM-BASED THERAPY

ARM A OR B

CYCLE N°: |__|__| **DAY:** |__|__| **DATE OF DISPENSATION :** |__|__| |__|__| |__|__|__|__|

- **METHOTREXATE**

Dispenser's Initials	Dose level (mg/m²)	Dose dispensed (mg)	Number of vials 50 mg / 2 mL	Date control CRA
	|__|__|__|	|__|__|__|	|__|__|	
When possible, please use the vials **in chronological order** and stick here the labels.				

*Comments :*_____

_____

Date : |__|__| |__|__| |__|__|__|__|

INVESTIGATOR/PHARMACIST:

Name : _____ ***Signature :***

C.R.A.:

Name : _____ ***Signature :***

Appendix 7: EORTC questionnaire

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |__||__||__||__|

Your birthdate (Day, Month, Year): |__|__||__|__||__|__|__|__|

Today's date (Day, Month, Year): 31 |__|__||__|__||__|__|__|__|

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you had trouble eating?	1	2	3	4
50. Have you had trouble eating in front of your family?	1	2	3	4
51. Have you had trouble eating in front of other people?	1	2	3	4
52. Have you had trouble enjoying your meals?	1	2	3	4
53. Have you had trouble talking to other people?	1	2	3	4
54. Have you had trouble talking on the telephone?	1	2	3	4
55. Have you had trouble having social contact with your family?	1	2	3	4
56. Have you had trouble having social contact with friends?	1	2	3	4
57. Have you had trouble going out in public?	1	2	3	4
58. Have you had trouble having physical contact with family or friends?	1	2	3	4
59. Have you felt less interest in sex?	1	2	3	4
60. Have you felt less sexual enjoyment?	1	2	3	4

During the past week:	No	Yes
61. Have you used pain-killers?	1	2
62. Have you taken any nutritional supplements (excluding vitamins)?	1	2
63. Have you used a feeding tube?	1	2
64. Have you lost weight?	1	2
65. Have you gained weight?	1	2

Appendix 8: Inducers or inhibitors of CYP3A4

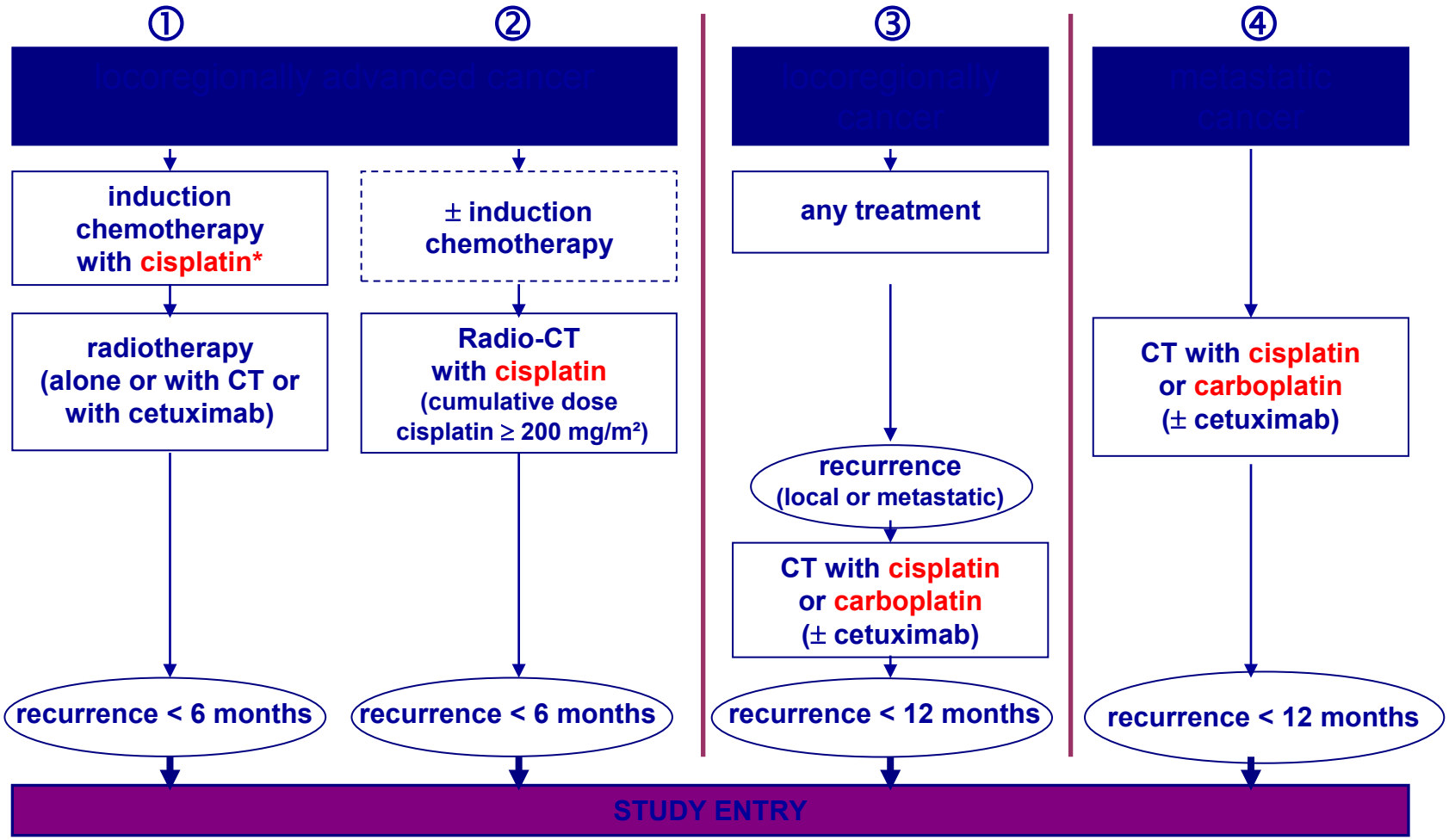
Non-exhaustive list of inducers and inhibitors of CYP 3A4

These treatments should be stopped at least 4 days before the 1st drug administration of **the pharmacokinetic study** However, their topical form is authorised.
They are allowed, if necessary during the **compassionate use** of vinflunine.

Inducers of isoform cytochrome P450 3A4
Millepertuis (Hypericum ; St John's Wort)
Antiepileptic *Barbiturate:* Phenobarbital, Primidone *Non barbiturate:* Phenytoin, Carbamazepine, Oxcarbazepine
Antiretroviral Efavirenz, Nevirapine
Antifungal Griseofulvin
Antimycobacterial Rifabutin, Rifampicin
Corticosteroid Dexamethasone
Antihypertensive Bosentan
Antidepressant Fluvoxamine
Inhibitors of isoform of cytochrome P450 3A4
Grape fruit juice
Antiretroviral Amprenavir, Delavirdine, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Atazanavir, Darunavir
Antibacterial *Macrolide:* Troleandromycin, Erythromycin, Telithromycin, Clarithromycin Chloramphenicol
Antimycobacterial Isoniazid
Antifungal *Triazole:* Fluconazole, Itraconazole, Voriconazole *Imidazole:* Ketoconazole, Miconazole
Oestrogen Ethinylestradiol
Androgen Danazol
Calcium-channel blocker Diltiazem, Nicardipine, Verapamil
Anti-arrhythmic agent Amiodarone
Leukotriene antagonist Zafirlukast

Reference list
Hansten P.H, Horn J.R.
The top 100 drug interactions. A guide to patient management, 2007 Edition, H&H Publication
Affsaps
Referenciel national des interactions médicamenteuses – Interactions médicamenteuses et cytochromes, April 2005.

Appendix 9: Diagram of categories of eligible patients according to inclusion criterion no.3



CT = chemotherapy

** cisplatin + 5-FU or docetaxel + cisplatin + 5-FU*