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STATISTICAL ANALYSIS PLAN

Compound Number : L00070
Name of Test Drug : i.v. Vinflunine (Javlor®)
Study code : L00070 IN 309 F0
Title of the study:

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

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Reasons for change: **Modification according to the protocol amendment (PA11)**
Simplification of analyses due to study early termination

SIGNATURES

	Title	Name (First & Last name)	Consistency between SAP and study protocol	Date	Signature
Author	**Statistician**	Benjamin POIRIER (Axiodis)	**NA**	23/11/2017	
Reviewer	**Clinical Study Physician**	Zahida ISSIAKHEM, MD	**NA**	24/11/2017	
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LIST OF ABBREVIATIONS AND DEFINITIONS

AEs	Adverse Events
AEOSI	Adverse Events Of Special Interest
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BSA	Body Surface Area
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridisation
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DI	Dose Intensity
EGFR	Epidermic Growth Factor Receptor.
EORTC	European Organisation for Research and Treatment of Cancer
ER	Estrogen Receptor
FISH	Fluorescent In Situ Hybridisation
FN	Febrile Neutropenia
HB	Haemoglobin
HLGT	High Level Group Term
HLT	High Level Term
HR	Hormone Receptor
i.v.	Intravenous
IDMC	Independent Data Monitoring Committee
IHC	Immunohistochemistry
ITT	Intent-To-Treat
LLT	Lowest Level Term
MedDRA	MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES
MTX	Methotrexate
ORR	Objective Response Rate
OS	Overall Survival
PD	Progression Disease
PDI	Planned Dose Intensity
PgR	Progesterone Receptor
PLT	Platelets

PR	Partial Response
PS	Performance Status
PFS	Progression-Free Survival
PRES	Posterior Reversible Encephalopathy Syndrome
PT	Preferred Term
pt (s)	Patient (s)
QoL	Quality of Life
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCCHN	Squamous Cell Cracinoma of Head and Neck
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIADH	Syndrome of Inappropriate Anti-Diuretic Hormone Secretion
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TTF	Time to Treatment Failure
ULN	Upper Limit of Normal
VFL	Vinflunine
WBC	White Blood Cells
WHO	World Health Organisation
Wk(s)	Week(s)

1. STUDY OBJECTIVES

The primary objective of the trial was to compare the overall survival of the i.v. vinflunine in combination with methotrexate versus methotrexate alone in incurable recurrent/metastatic squamous cell carcinoma of the head and neck (SCCHN) patients who have failed platinum-based chemotherapy.

The results of the 2nd interim analysis (August 2015) of efficacy have led the IDMC to recommend the implementation of a futility analysis of overall survival which is the primary endpoint of study 309. This futility analysis was carried out by IDDI, a CRO expert in biostatistics, independently from the sponsor and the results reviewed by the IDMC.

The results of the futility 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, Pierre Fabre has decided to stop the recruitment of study patients on 16th October 2015.

This SAP is aimed to adapt the statistical analysis according to the protocol amendment 11.

2. STUDY DESIGN

This multicentre, open-label, randomized, Phase III study will enrol 530 patients with SCCHN who have failed platinum-based chemotherapy. Patients will be randomised in a 1:1 ratio to receive i.v. vinflunine plus methotrexate (arm A) or methotrexate alone (arm B).

Randomisation will be stratified according to a minimisation procedure (**Pocock SJ, 1975**):

- 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 randomised to receive:

- Arm A : i.v. vinflunine 280 mg/m² on day 1 and methotrexate 30 mg/m^2 on days 1 and 8 every 3 weeks.
- Arm B : methotrexate 40 mg/m^2/week.

Overall survival (OS) 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 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. 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.

3. SAMPLE SIZE

The primary objective of the study was to show that the vinflunine plus methotrexate (arm A) is superior to methotrexate alone (arm B) in terms of overall survival. The final analysis will require at least 437 deaths; this is the number of events needed for a two sided, log-rank test at an alpha = 0.05 significance level to have 90% power to show a statistically significant difference when the true hazard ratio is 0.733 (i.e., when the median OS in the vinflunine arm is 7.5 months and the median OS in the control arm is 5.5 months). An expected total number of 530 patients was planned. It was estimated that the study will take approximately 19 months to accrue and the OS analysis is expected to be performed ten months following the last patient accrued. The anticipated lost to follow-up is estimated to be 5%.

Following the decision to stop the recruitment:

- The statistical analysis will actually be conducted on the 459 randomised patients.
- 325 events should be observed 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.

4. EFFICACY PARAMETERS

Tumour assessment will be performed according to the revised RECIST guidelines version 1.1 (Therasse P, 2000, Eisenhauer E, 2009). Assessment of all lesions was planned to be carried out at baseline then every 6 weeks (+/- 3 working days) until disease progression, regardless of the timing of the treatment cycles and whatever the treatment administered.

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 is documented, then survival information was collected approximately every month for the first 6 months and then every 3 months until death.

For patient who discontinued the study treatment due to PD, survival information was collected approximately every month for the first 6 months and then every 3 months until death.

According to the protocol amendment 11, no follow-up visit will be performed. At the time of this amendment:

- patients under treatment will stop the study at the EOT
- patients under follow-up will stop immediately

The end of study is defined as the date of the last study treatment plus 30 days for the last patient on treatment (EOT of the last patient).

4.1. PRIMARY EFFICACY PARAMETERS

4.1.1. Overall survival

The primary efficacy parameter is overall survival defined as the time from randomization 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.

4.2. 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

4.2.1. 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.

4.2.2. Objective response rate

The best overall response of patients is defined as the best response designation recorded across all time points from the date of randomisation until disease progression. Overall best responses assessed after the end of study period (last administration + 30 days) will not be reported in the response rate.

No confirmation will be needed for the best overall response.

If a patient had to end the treatment because of progression before the first assessment, he/she will be considered early progressive and the best overall response of the patient will be considered as progression.

The objective Response Rate (ORR) is defined as a percentage of complete and partial responses (CR and PR) observed in the population analysed:

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

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.

4.2.3. Disease control rate

Disease control rate (DCR) is defined as a percentage of best overall responses CR, PR and SD in the analysed population:

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

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.

Of note, patients with only non-measurable disease at baseline assigned a best overall response of Non-CR/non-PD, will not be considered as stable and will not be counted as patient having disease control (Table 4-1).

Table 4-1: 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

4.2.4. Duration of response

The duration of objective response will be measured for responders (CR + PR) from the time that measurement criteria are first met for complete or partial response (whichever status is recorded first), until the first date that recurrent or progressive disease is objectively documented or the date of death due to any cause. The duration of response of 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 overall response will be censored at the date of first administration of the new anti-cancer treatment.

Following the protocol amendment 11, the number of censored patient will be higher than expected. The result should be interpreted with cautiously.

4.2.5. 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. The duration of disease control of 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.

Following the protocol amendment 11, the number of censored patient will be higher than expected. The result should be interpreted with cautiously.

4.2.6. 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.

Following the protocol amendment 11, the number of censored patient will be higher than expected. The result should be interpreted with cautiously.

4.2.7. Time to first response

Time to first response will be calculated among the responders (i.e. CR and PR) from the randomisation date up to the date of first documented CR or PR.

Following the protocol amendment 11, the number of censored patient will be higher than expected. The result should be interpreted with cautiously.

5. SAFETY PARAMETERS

5.1. ADVERSE EVENTS

Each patient will be assessed for occurrence of adverse events. The CTCAE version 3.0 (publish date 9 Aug 2006) will be used. Adverse events not classified by the CTCAE will also be reported and graded according to their severity: mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), sudden death (grade 5), not applicable in case of progression or adverse event not gradable according to CTCAE and leading to dose modification (NA).

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

- Any increase in the grade (according to CTCAE) compared to baseline sign or symptom, or
- Any sign or symptom becoming serious during the study period, or
- Any sign or symptom requiring a modification of the study drug administration, or
- Any sign or symptom becoming possibly, probably or definitely related to the study drug

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

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

- the worst grade of the adverse events during the pre-study period (within 2 weeks prior to treatment),
- the seriousness of the event during the pre-study period,

This situation will be used as comparator to determine whether an existing adverse event during study period becomes treatment-emergent.

The adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA). The implementation of this international terminology in the Oracle Clinical® database will be performed using the available version of MedDRA (Version 19.0). Each description of the toxicity (verbatim) will be associated with the five following items:

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

Two sets of events will be considered:

- all adverse events regardless of relationship to treatment,
- the adverse events that are possibly, probably or definitely related to treatment,

*Of note, if the causality is **missing**, the AE will be considered as **related** to study treatment*

A patient will be evaluable for non-haematological toxicity if at least one drop of any treatment was given and the toxicity has been assessed by the investigator. The patient will be analysed in the treatment arm he/she was effectively treated.

5.1.1. Adverse Events Of Special Interest

Adverse Events Of Special Interest (AEOSI) will be presented to facilitate monitoring of the following MedDRA preferred terms or Highest Level Terms of special interest: Myelosupression, Febrile Neutropenia, Infections with severe neutropenia: clinically relevant Infections (potential bacterial origin), Constipation, Ileus, Intestinal obstruction, Abdominal pain, Nausea, Vomiting, Stomatitis / Mucositis, Diarrhoea, Myocardial infarction/ Ischemia, Cardiac arrhythmias, Cardiac conduction disorders, Local injection/infusion site reactions, Extravasation, Peripheral sensory neuropathy, Peripheral motor neuropathy, Autonomic neuropathy, Asthenia/fatigue, Myalgia, Immediate hypersensitivity, SIADH, PRES, Hepatic dysfunction,.

AEOSI will be programmatically determined from a predefined list presented in appendix 3.

5.1.2. Serious Adverse Event

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 seriousness criteria should be reported as a SAE.

Any pregnancy occurring after patient exposure to study drug(s), should be reported on the SAE notification form.

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.

5.2. FEBRILE NEUTROPENIA

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

5.3. HAEMATOLOGICAL PARAMETERS

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

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

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

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

5.4. BIOCHEMICAL PARAMETERS

Biochemical toxicity will be assessed by laboratory investigations of liver function tests (i.e. total bilirubin, alkaline phosphatase, AST, ALT), renal function tests (creatinine and calculated (Cockroft-Gault formula) creatinine clearance) and glucose, total proteins, albumin, urea, sodium, potassium, calcium, bicarbonate, magnesium, chloride. Grades will be calculated according to the CTCAE version 3.0.

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

- At least one drop of any treatment has been administered,

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

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

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

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

6. OTHER PARAMETERS

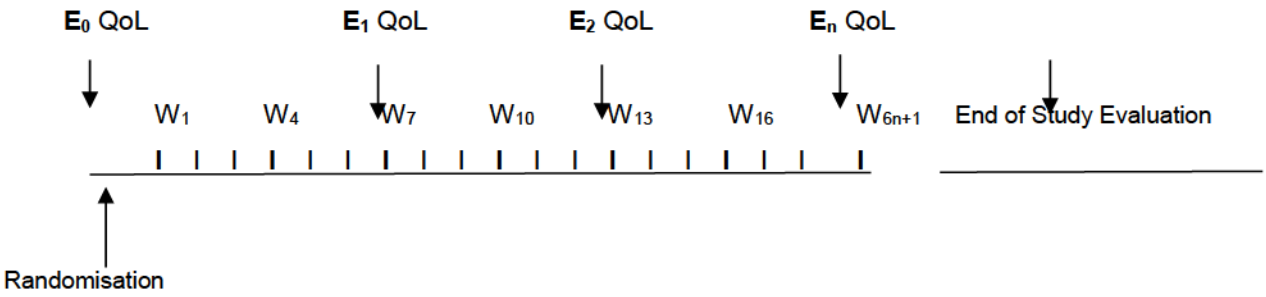
6.1. CONCOMITANT MEDICATIONS

In the same way as the adverse events, concomitant medications will be coded using the specific international terminology WHO-Drug Dictionary version 2011, Q2.

6.2. QUALITY OF LIFE PARAMETERS

The European Organisation for Research and Treatment of Cancer (EORTC) score questionnaire (QLQ-C30) will be analysed as well as the QLQ-Head and Neck 35 EORTC module, to measure the health-related quality of life.

The QLQ-C30 and the QLQ-Head and Neck 35 EORTC module will be completed prior to randomization, every 6 weeks and at the end of treatment evaluation.



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.

Of note, a higher value in functional scales will reflect a better level of function, but for “symptoms” scales a higher value will reveal a deterioration of the condition.

Each scale in the EORTC QLQ-C30 questionnaire will be scored (0 to 100) according to the EORTC recommendations in the EORTC QLQ-C30 Scoring Manual. The scoring method is summarized below. In this summary Qi refers to the i^{th} question on the EORTC QLQ-C30.

Functional scales:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status:

- Global health status/QOL: ((Q29+Q30)/2-1)/6 * 100

Symptom scales/Items:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnoea: ((Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhoea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

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.

Each scale in the QLQ-H&N 35 EORTC questionnaire will be scored (0 to 100).The scoring approach for the QLQ-H&N35 is identical in principle to that for the symptom scales /single items of the QLQ-C30 and is summarized below. In this summary Qi refers to the i^{th} question on the QLQ-H&N 35 EORTC.

Multi-item scales/Items:

- Pain: ((Q1+Q2+Q3+Q4)/4-1)/3 * 100
- Swallowing: ((Q5+Q6+Q7+Q8)/4-1)/3 * 100
- Senses problems: ((Q13+Q14)/2-1)/3 * 100
- Speech problems: ((Q16+Q23+Q24)/3-1)/3 * 100

Trouble with social eating: ((Q19+Q20+Q21+Q22)/4-1)/3 * 100
Trouble with social contact: ((Q18+Q25+Q26+Q27+Q28)/5-1)/3 * 100
Less sexuality: ((Q29+Q30)/2-1)/3 * 100

Single items:

Teeth: (Q9-1)/3 * 100
Opening mouth: (Q10-1)/3 * 100
Dry mouth: (Q11-1)/3 * 100
Sticky saliva: (Q12-1)/3 * 100
Coughing: (Q15-1)/3 * 100
Felt ill: (Q17-1)/3 * 100
Pain killers : (Q31-1)/3 * 100
Nutritional supplements: (Q32-1)/3 * 100
Feeding tube: (Q33-1)/3 * 100
Weight loss: (Q34-1)/3 * 100
Weight gain: (Q35-1)/3 * 100

If a question was filled in by circling more than one answer, the internal convention at Pierre Fabre is to consider the answer as missing.

A questionnaire is considered to be completed if more than two thirds of the questions are answered. Otherwise the questionnaire is ignored for the analysis.

6.2.1. Primary parameter

The primary quality of life parameter will be the global health status.

6.2.2. Secondary parameter

The secondary quality of life parameters will be the fourteen other scales of QLQ-C30 questionnaire and the eighteen scales of the QLQ-H&N 35 EORTC. Each analysis will be presented by functional and/or “symptoms” scales for QLQ-C30 questionnaire and by multi-items scales and/or single items for the QLQ-H&N 35 EORTC.

6.2.3. Windows

The Quality of life of a patient at the time of an administration will be based on the answers provided by the patient in the last questionnaire completed and evaluable.

At baseline, only questionnaires which were completed within the window of seven days prior to the randomisation (and including any questionnaire filled that day) will be considered. If more than one questionnaire is available within this window the last non-missing questionnaire will be analysed.

Any questionnaire that would be completed after the date of last administration plus 30 days therefore out of study treatment (not as per protocol) would not be analysed.

6.3. FURTHER ANTI-CANCER THERAPY

Further anti-cancer therapies include any anti-tumour treatment given to the patient after withdrawal from study drug treatment.

7. DEFINITION OF POPULATIONS

7.1. 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.

7.2. ELIGIBLE POPULATION

Following the protocol amendment 11, the eligible population will not be defined and used.

7.3. EVALUABLE POPULATION FOR RESPONSE

Following the protocol amendment 11, the evaluable population for response will not be defined and used.

7.4. EVALUABLE POPULATION FOR SAFETY

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

7.5. EVALUABLE POPULATION FOR HEALTH-RELATED QUALITY OF LIFE ASSESSMENT

7.5.1. Evaluable population for QLQ-C30

To be evaluable for the QLQ-C30 questionnaire, randomised patients should have completed at least two thirds (i.e. at least 20 questions) of the questions of the baseline QLQ-C30 questionnaire within 7 days prior to randomisation, and at least two thirds of the questions of a QLQ-C30 questionnaire during the study period or at the end of study (during last cycle).

7.5.2. Evaluable population for QLQ-H&N 35 EORTC module

To be evaluable for the QLQ-H&N 35 EORTC module, randomised patients should have completed at least two thirds of the questions (i.e. at least 23 questions) of the baseline the QLQ-H&N 35 EORTC

module within 7 days prior to randomisation, and at least two thirds of the questions of a QLQ-H&N 35 EORTC module during the study period or at the end of study (during last cycle).

8. STATISTICAL METHODS

8.1. STATISTICAL SOFTWARE AND METHODOLOGY

The statistical analysis will be performed by Institut de Recherche Pierre Fabre. Data will be analysed using the SAS• system software version 9.4 (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.

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

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

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

8.2. STATISTICAL METHODS FOR CATEGORICAL VARIABLES

The •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.

8.3. STATISTICAL METHODS FOR ORDINAL VARIABLES

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

8.4. STATISTICAL METHODS FOR CONTINUOUS VARIABLES

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

8.5. STATISTICAL METHODS FOR TIME DEPENDENT DATA

To describe time dependent parameters, Kaplan-Meier curves and life tables by treatment arm will be provided. Confidence intervals on the median will be calculated using the Brookmeyer and Crowley method. Hazard ratio and 95% confidence intervals will be reported. A stratified Cox proportional model will be performed to compare the two treatment arms taking into account the stratification factors (except center) used at the time of randomisation.

According to the protocol amendment 11, no multivariate analysis will be performed.

8.6. STATISTICAL METHODS FOR HEALTH-RELATED QUALITY OF LIFE DATA

Following the protocol amendment 11, no repeated measure analysis will be performed.

9. TREATMENT GROUP DESCRIPTION

9.1. DESCRIPTION AT BASELINE

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

9.1.1. Overview of the study

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

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

The number of patients randomised, treated (evaluable for safety) and evaluable for quality of life will be presented by treatment group. Patients with at least one protocol deviations will be tabulated by treatment arm and by type of protocol deviation.

For arm A, the treatment duration is defined as the time elapsed between the date of 1st administration and the date of the last VFL administration (if MTX not given) + 21 days or the date of the last MTX administration (if given) + 14 days. For arm B, the treatment duration is defined as the time elapsed between the date of the 1st administration and the date of the last D1 administration of the last cycle + 21 days (if D8 and D15 not given) or the date of the last D8 administration of the last cycle + 14 days (if D15 not given) or the date of the last D15 administration of the last cycle + 7 days (if D15 given). Treatment duration will be tabulated by treatment arm.

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

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

9.1.2. Characteristics at baseline

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

Demographic data

- Age at the time of randomisation
- Categorized groups of age :< 35, [35 – 50[, [50 – 65[, [65 – 75[, [75 – 80[and ≥ 80 years
- Sex
- Body weight,
- WHO Performance Status

Stratification data Extract from the IWRS database

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

Tumour characteristics at diagnosis

- Anatomic site of cancer,
- Histopathological grade,
- TNM classification,
- Stage,

Tumour characteristics at study entry

- Extent of the disease at study entry,
- Patient category,
- Interval from diagnosis to study entry (randomisation),
- Categorized groups of Interval from diagnosis to study entry (< 2 years vs. ≥ 2 years),
- **Progression-free interval***,
- Categorized groups of progression-free interval (< 6 months vs. ≥ 6 months),
- **Treatment free interval****,
- Categorized groups of treatment free interval (< 6 months vs. ≥ 6 months),
- **Disease free interval*****
- Categorized groups of disease free interval** : <2 years, ≥ 2 years,
- Presence of visceral involvement (lung +/- liver),
- Presence of visceral involvement (such as liver, lung, pleura, heart, pericardium, kidney, thyroid and suprarenal gland, detailed list in appendix 4)
- Categorized groups of number of organs involved: 1, 2 and • 3 organs,

- Detail of organs involved, grouping provided in appendix 4
- Measurable/non-measurable disease****.

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

*** : The **treatment free interval** is the time elapsed between the date of end of the last treatment (prior chemotherapy, prior radiotherapy, prior treatment with cetuximab, whichever occurs last) and the first administration of study treatment.*

****The **disease free interval** is the time interval elapsed between the date of end of the last prior chemotherapy according to intents induction/concomitant with radiotherapy and the date of relapse or progression.*

***** **Measurable disease** defined as:*

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

Prior therapy

An overview of prior therapies for SCCHN will be provided giving:

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

Surgery

- Details of surgeries using MedDRA system organ class and preferred term,

Radiotherapy

- Number of patients who underwent a radiotherapy (for SCCHN) with intent and intent of last radiotherapy,

Chemotherapy

Number of patients who underwent a chemotherapy (for SCCHN) with intent and intent of last chemotherapy,

Number of lines,

Number of patients treated with a prior platinum agent (Cisplatin, Carboplatin, …),

Type of prior platinum-based chemotherapy by intent

Number of refractory/resistant/other failure patients by intent for prior platinum-based chemotherapy

Class of prior adjuvant/induction chemotherapy: (Platinum single agent, Platinum + Taxane, Platinum + Other, Taxane single agent, Taxane + Other)

Class of prior metastatic chemotherapy: (Platinum single agent, Platinum + Taxane, Platinum + Other, Taxane single agent, Taxane + Other)

Number of cycles of chemotherapy by intent and by class of chemotherapy,

Best response of the last chemotherapy by intent and by class of chemotherapy,

Other prior treatments

Number of patients who underwent a treatment with cetuximab (including panitumumab) with intent and intent of last treatment,

Number of patients who underwent a prior treatment with other antineoplastic drugs with intent,

Clinical examination

Electrocardiogram (normal/abnormal but not clinically significant/abnormal clinically significant),

Baseline biological abnormalities,

Baseline haematological abnormalities.

Temperature, Blood Pressure, Pulse

Concomitant medications at baseline

Concomitant medications whatever the indication, according to the WHO-Drug dictionary,

Concomitant medications with a tumour related indication, according to the WHO-Drug dictionary,

Concomitant medications with a prophylactic indication, according to the WHO-Drug dictionary

Concomitant medications with pre-treatment event indication, according to the WHO-Drug dictionary,

Concomitant medications with a medical history indication,

Prior medical history

Prior medical history according to MedDRA System Organ Classification (SOC) and Preferred Term (PT),

Listing of prior medical or surgical history,

Pre-treatment events

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

Listing of Pre-treatment events at baseline.

9.2. DESCRIPTION DURING THE STUDY

Description during the study will be done on all treated population.

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

- Duration of exposure,
- Number of patient with at least one dose permanently discontinued,
- Number of patient with at least one dose cancelled,
- Number of patients with at least one dose reduced,
- Number of patients with at least one dose delayed,
- Number of patients with at least one infusion interrupted.

The total number of cycles given during the study, the median number of cycles as well as the number of patients by cycle will be given. The number of methotrexate administration will be presented in each arm.

The actual dose of (mg/m²) will be calculated from the total dose administered (mg) divided by the BSA.

The BSA will be recalculated at each cycle.

The Body Surface Area (BSA) will be calculated as follows :

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

where :

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

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

The following categories of vinflunine doses will be used:

Table 9-1 : Categorized dose of vinflunine

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

The following categories of methotrexate doses will be used:

Table 9-2 : Categorized dose of methotrexate

Dose category in mg/m²	Dose of methotrexate in mg/m²
>40	] 45 - • [
40	] 35 - 45]
30	] 25 – 35]
20	] 15 - 25]
<20	] 0 - 15]

The dose intensity (mg/m²/wk) and relative dose intensity (%) will be calculated per patient and per cycle for each treatment drug. Cumulative dose of vinflunine or methotrexate (mg/m²) will also be provided per patient. Descriptive statistics such as median and range will be provided.

Moreover, for both treatment arms, relative dose intensity will be categorised (< 50%, [50% -70%[, [70% - 90%[, [90% - 110%[, ≥ 110%) per patient and per cycle.

9.2.1. Dose intensity per cycle

Actual dose intensity per cycle will be defined as follows :

$$\text{DI at cycle } i = \frac{\text{Actual dose received at cycle } i}{\text{Actual duration of cycle } i \text{ (wk)}} = \frac{\text{Actual dose received at cycle } i}{[(\text{Course date at cycle } i+1) - (\text{Course date at cycle } i)]}$$

The cycle duration at cycle n will be equal to the time elapsed between the day 1 administration date of cycle n and the day 1 administration date of cycle n+1. The duration of the last cycle will be estimated to be 3 weeks.

9.2.2. Relative dose intensity per cycle

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

$$\text{RDI at cycle } i = \left(\frac{\text{DI at cycle } i}{\text{PDI}}\right) \cdot 100 = \left(\frac{\text{Actual dose intensity at cycle } i}{\text{Planned dose intensity}}\right) \cdot 100$$

where :

$$\text{PDI at cycle } i = \frac{\text{Planned dose}}{\text{Theorical duration of cycle } i \text{ (wk)}}$$

The theoretical cycle duration is 3 weeks. The planned dose for each drug is defined as follow:

Table 9-3: Planned dose intensity in mg/m²/wk of vinflunine

Planned Dose (mg/m²) per cycle	Cycle duration (wk)	P.D.I (mg/m²/wk)
280	3	93.33

Table 9-4: Planned dose intensity in mg/m²/wk of methotrexate

Treatment arm	Planned Dose (mg/m²) per cycle	Cycle duration (wk)	P.D.I (mg/m²/wk)
Arm A	60	3	20
Arm B	120	3	40

9.2.3. Dose intensity per patient

Actual dose intensity per patient will be defined as follows:

$$DI = \frac{\text{Cumulative dose}}{\text{Treatment duration (wk)}} = \frac{\sum_{i=1}^{n} dose\,i}{\sum_{i=1}^{n} duration\,i}$$

where:

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

9.2.4. Relative dose intensity per patient

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

$$RDI = \left(\frac{DI}{PDI}\right) \cdot 100 = \left(\frac{\text{Actual dose intensity}}{\text{Planned dose intensity}}\right) \cdot 100$$

PDI is defined for each arm in the section 9.2.2.

9.2.5. Dose reductions

Dose reductions are allowed by the study protocol. The number of patients and cycles with a dose reduction in each arm will be presented as well as the reasons.

9.2.5.1. Vinflunine dose reduction (Arm A)

- Number of patients with at least one dose of vinflunine reduced at day 1.
- Number of cycles with a dose of vinflunine reduced at day 1.
- Reasons for vinflunine dose reduction:

Reason for dose reduction of vinflunine	Dose reduction as per protocol				N cycles	
	From 280 to 250 mg/m²		From 250 to 225 mg/m²			
	N	%	N	%	N	%
Adverse Event Other						

Listing of the reasons for vinflunine dose reduction in arm A.

9.2.5.2.Methotrexate dose reductions

Number of patients with at least one dose reduction of methotrexate:

Number of cycles with at least dose reduction of methotrexate:

Number of administrations with a dose reduction of methotrexate:

Reasons for methotrexate dose reductions (as per protocol) in arm A:

Reason for dose reduction	Dose reduction as per protocol (from X to Y) in mg/m²		N cycles
	30 20	30 <20	
	N(%)	N(%)	N(%)
Adverse Event Other			

Reasons for methotrexate dose reductions (as per protocol) in arm B:

Reason for dose reduction	Dose reduction as per protocol (from X to Y) in mg/m²						N cycles
	40 30	40 20	40 <20	30 20	30 <20	20 <20	
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Adverse Event Other							

Listing of the reasons for methotrexate dose reductions,

The format of the tables may be slightly modified according to observed data.

9.2.6. Treatment cancellation

Cancellation of day 1 vinflunine administration is not allowed by the protocol. Methotrexate dosing may be cancelled in both arms (D8 in Arm A and D8/D15 in Arm B) as per protocol (§ 5.2.3 and § 5.2.4 of the protocol).

The number of cycles with at least one day of methotrexate cancelled and number of patients with at least one day of dosing cancelled will be displayed. Reasons for treatment cancellation will be provided.

Number of patients with at least one methotrexate dose cancelled,

Number of cycles with at least one methotrexate dose cancelled,

- Reasons for methotrexate on D1 / D8 / D15 dose cancellation, per patient and per cycle,
- Listing of methotrexate dose cancelled and reason,

If cancellation are observed for Vinflunine, they will be described in the same way as for Methotrexate.

9.2.7. Dose interruption

For both arms, the number of patients and cycles with an infusion interruption will be presented as well as the reasons.

- Number of patients with at least one infusion interruption,
- Number of cycles with at least one infusion interruption,
- Reasons for infusion interruption,
- Listing of the reasons for infusion interruption,

9.2.8. Treatment delay

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

A treatment cycle will be considered as delayed if administered ≥ 4 days after the planned date with a three weeks interval from day 1 of previous cycle.

The delays will be categorized as follows:

- [4 – 7 days[,
- [7 – 14 days[,
- • 14 days.

The following information will be described:

- Number of patients with at least one cycle delayed by four days or more, by arm
- Number of cycles delayed, by arm
- Categorized groups of cycle delay, by arm
- Reasons for cycle delay of four days or more, by arm
- Listing of the cycles delayed with reasons,

9.2.9. Dose discontinuations

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 following information will be provided for patients treated in arm A:

- Number of patients and cycles with discontinuation of vinflunine or methotrexate (arm A),

Number of cycles, cumulative dose (by patient), dose intensity (by patient) and relative dose intensity (by patient) of vinflunine / methotrexate given in monotherapy,

Listing of patients with discontinuation of vinflunine or methotrexate with drug administration for cycles given in monotherapy (arm A),

9.2.10. Route of administration and setting

The route of vinflunine and methotrexate administration and setting will be presented by patient and by cycle.

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

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

Route of administration by cycle:

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

Route of administration by administration (Methotrexate only)

Courses	**Arm A**		**Arm B**	
	Central venous line N (%)	**Peripheral vein N (%)**	**Central venous line N (%)**	**Peripheral vein N (%)**
Number of administrations of MTX				

9.2.11. Concomitant medications

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

10. EFFICACY ANALYSES

10.1. PRIMARY EFFICACY ANALYSIS

The final analysis of overall survival was planned to be conducted once the required number of events (437 deaths) has been observed. The statistical analysis will actually be conducted on the 459 randomised patients.

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

The hypothesis of superiority in terms of OS of vinflunine in combination with methotrexate versus methotrexate alone will be accepted if the p-value from a stratified log-rank test is smaller than 0.05. The stratification factors will be:

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

Centre will not be used for the analysis because of the high number of participating centres.

The stratified log-rank test, hazard ratio and 95% confidence interval of the hazard ratio will be computed using the SAS® procedure «PHREG». The treatment arm will be entered as a covariate in the Cox proportional hazard model and the variables of stratification at randomisation (except centre) will be entered as stratification factors in the model.

10.2. SUPPORTIVE ANALYSIS OF THE PRIMARY EFFICACY PARAMETER

According to the protocol amendment 11, no supportive analysis of the primary efficacy parameter will be performed.

10.3. SENSITIVITY ANALYSES OF THE PRIMARY EFFICACY PARAMETER

According to the protocol amendment 11, no sensitive analysis of the primary efficacy parameter will be performed.

10.4. SECONDARY EFFICACY ANALYSES

10.4.1. Progression Free Survival

The analysis of Progression Free Survival (PFS) will be conducted in the ITT population.

10.4.1.1. Primary analysis of PFS

The primary analysis of PFS will be done in the ITT. The stratified log-rank test, hazard ratio and 95% confidence interval of the hazard ratio will be computed using the SAS® procedure «PHREG». The treatment arm will be entered as a covariate in the Cox proportional hazard model and the variables of stratification at randomisation (except centre) will be entered as stratification factors in the model.

10.4.2. Tumour response

The analyses of tumour response will be performed in the ITT population.

10.4.2.1. Objective response rate and disease control rate

Objective Response Rate (ORR) and Disease Control Rate (DCR) 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.

10.4.2.2. Duration of overall response and disease control

Duration of response and duration of disease control will be analysed on the ITT population. A stratified log-rank test will be used to compare the two treatment arms. The stratification factors will be those defined above.

10.4.2.3. Time to first response

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

10.4.2.4. Time to treatment failure

The time to treatment failure will be described in the ITT population. No formal statistical comparisons are planned.

10.4.3. Subgroups analyses

Following the protocol amendment 11, no subgroup analysis of Overall Survival, Progression-Free Survival, DCR and ORR will be performed.

11. SAFETY ANALYSES

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

11.1. OVERVIEW OF THE SAFETY

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

For definition of evaluable patient for non-haematological and evaluable cycle/patient for haematological and biochemistrical toxicity, see § 5.1 , § 5.3 and §5.4, respectively.

11.2. ADVERSE EVENTS

11.2.1. All adverse events

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

A summary table will provide by treatment arm the following:

- On treatment deaths
- Patients with at least one AE
- Patients with at least one TEAE
- Patients with at least one SAE
- Patients with at least one related TEAE
- Patients with at least one related TESAE
- Patients with at least one TEAE leading to discontinuation
- Patients with at least one TEAE requiring dose interruption and/or adjustment
  - Patients with at least one TEAE requiring dose interruption
  - Patients with at least one TEAE requiring dose adjustment
- Patients with at least one TEAE requiring additional therapy
- Cycles with at least one AE
- Cycles with at least one TEAE

For all these items, the overall incidence, the incidence of grade 3/4, the incidence of grade 5 and the incidence of grade NA will be provided.

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

Of note, some laboratory toxicities will be presented in the non-haematological adverse event tables when reported as adverse events as per study completion guidelines. However, biochemical and haematological event should be interpreted from the tables described in section 5.1

11.2.2. Selected adverse events

The worst CTCAE grade per patient of Adverse Events Of Special Interest (AEOSI) listed in section 5.1. will be presented for patients treated in both arms and regarding the relationship to treatment.

11.2.3. Serious adverse events

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

A listing of the serious toxicities will also be provided with the following variables: patient number, cycle number, seriousness, CTCAE grade, relationship to treatment, date of onset, date ceased and significant consequences.

11.2.4. Deaths

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

Two listings will be provided depicting the patients who died:

patients who died within 30 days after the last administration,
patients who died more than 30 days after the last administration.

These listings will contain the following variables: patient number, cycle number, date of death, reason of death, source of information.

11.3. LABORATORY TESTS

11.3.1. Haematological toxicities

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

A first analysis will present the worst grade by patient and the worst grade experienced during a cycle. Cycles where a grade 3/4 haematological toxicity occurred will be listed by patient number. In a second analysis, the worst grade of patients according to the grade at baseline will be tabulated.

11.3.2. Biochemical toxicities

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

In order to examine the evolution of biochemical toxicities, worst CTCAE grade (hypo and hyper for metabolic function tests) will be analysed in relation to the grade presented by the patient at baseline. Cycles where grade 3/4 biochemical toxicity occurred will be listed by patient number.

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

12. OTHER ANALYSES

12.1. HEALTH-RELATED QUALITY OF LIFE ANALYSES

The analysis of health-related quality of life will be done for each questionnaire (EORTC QLQ-C30 and QLQ-Head and Neck 35 EORTC module) on each evaluable population.

12.1.1. Evaluable questionnaire

To be evaluable for health-related quality of life assessment, patients should have completed one questionnaire (at least two thirds of the questions) within seven days prior to randomisation, and at least one questionnaire (at least two thirds 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. For definition of evaluable population for QOL, see § 5.1.

At baseline, only questionnaires which were completed within the window of seven days prior to the day of randomisation (and including any questionnaire filled that day) will be considered. The end of study questionnaire needs to be filled in within 30 days after the last administration in order to be evaluable. Any later questionnaire will not be analysed.

If more than one questionnaire is available within an evaluation period the last non-missing questionnaire will be analysed.

12.1.2. Descriptive analyses

The number of QoL questionnaires completed and evaluable per evaluation will also be given.

The quality of life will be assessed (using the EORTC questionnaires, without any medical staff influence) at baseline before randomisation, every 6 weeks during the study and at the end of treatment evaluation (within 30 days of the last dose administration).

Missing data is a typical problem of QoL analysis. There are two levels of missing data :

- Missing item(s) in a questionnaire filled in by the patient,
- Completely missing questionnaire at a given evaluation.

For the first level, if more than one third of the items is missing then the questionnaire is non-evaluable.

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 for each (mean, standard deviation, median, Q1, Q3, minimum and maximum).

13. CHANGES INTERFERED SINCE LAST VERSION

According to the protocol amendment PA11 (05/02/2016) and the associated protocol version 7 (05/02/2016), the statistical analysis was reduced to:

- Description of study, patients and disease characteristics,
- Efficacy: analysis of the primary efficacy variable (OS) and the secondary efficacy endpoint on the ITT population only (no other efficacy population will be defined),
- Safety: exhaustive description of safety parameters.
- Other: description of Quality of Life.

Therefore, in order to perform an abbreviated Clinical Study Report (CSR), in comparison to the previous version of the SAP (version 3 dated 28/05/2014), the following analyses have been deleted:

- Analysis of primary and secondary efficacy criteria on other population than ITT,
- Analysis of efficacy criteria on subgroups of patients,
- Multivariate analyses of efficacy criteria,
- Description over time of values and changes from baseline for laboratory date, because CTCAE grades will be provided,
- Some detailed tables of disease history, prior therapies and concomitant medications, limiting the analyses to an overview of the safety and patients and disease characteristics,
- Other analyses including clinical benefit, further anti-cancer therapy, pharmacoeconomic analyses.

Summary tables of adverse events, prior therapies for SCCHN and exposure have been added.

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

14. REFERENCES

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15. APPENDICES

Appendix 1: LIST OF TABLES, LISTINGS AND FIGURES

Appendix 2: STATISTICAL ANALYSIS CONVENTIONS

Appendix 3: ADVERSE EVENTS OF SPECIAL INTEREST

Appendix 4: ANALYSIS OF TUMOUR LOCATION AT BASELINE

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

SECTION	Title	RTF reference
10.1	Number of Patients enrolled, randomized, treated and evaluable for Quality of Life [All patients]	10_1a.RTF
10.1	Patient disposition [ITT]	10_1b.RTF
10.1	Patients with at least one Protocol deviations by type [ITT]	10_1c.RTF
11.2	Demographic data [ITT]	11_2_1.RTF
11.2	Stratification factors [ITT]	11_2_2.RTF
11.2	Disease History[ITT]	11_2_3.RTF
11.2	Summary of Prior therapies for SCCHN [ITT]	11_2_6.RTF
11.2	Prior therapies: chemotherapy [ITT]	11_2_7.RTF
11.2	Prior therapies: radiotherapy [ITT]	11_2_8.RTF
11.2	Prior therapies: surgeries by SOC and PT [ITT]	11_2_9.RTF
11.2	Prior therapies: Other therapies [ITT]	11_2_10.RTF
11.2	Clinical examinations at baseline [ITT]	11_2_11.RTF
11.2	Haematological CTCAE grades at study entry [ITT]	11_2_12.RTF
11.2	Biochemical CTCAE grades at study entry [ITT]	11_2_13.RTF
11.4.1.1	Overall Survival (OS-months) [ITT]	11_4_1_1.RTF
11.4.1.1	Overall Survival (OS-months) [ITT]	11_4_1_1_FIG.RTF
12.1	Summary of exposure [ITT]	12_1_1.RTF
12.1	Route of administration and settings by patient [ITT]	12_1_2.RTF
12.1	Route of administration and settings by cycle [ITT]	12_1_3.RTF
12.1	Exposure: Description of cycles [ITT]	12_1_4.RTF
12.1	Exposure: Cumulative dose, actual dose intensity and relative dose intensity by patient [ITT]	12_1_5.RTF
12.1	Exposure: Actual dose intensity and relative dose intensity by cycle [ITT]	12_1_6.RTF
12.1	Dose delayed and reasons [ITT]	12_1_7a.RTF
12.1	Listing of the reasons of dose delayed [ITT]	12_1_7b.RTF
12.1	Dose reduction of Vinflunine and reasons [ITT]	12_1_8a.RTF
12.1	Reasons by dose reduction of Vinflunine [ITT]	12_1_8b.RTF
12.1	Listing of the reasons of Vinflunine dose reductions [ITT]	12_1_8c.RTF
12.1	Dose reduction of Methotrexate and reasons [ITT]	12_1_8d.RTF
12.1	Reasons by dose reduction of Methotrexate in VFL+MTX group [ITT]	12_1_8e.RTF
12.1	Reasons by dose reduction of Methotrexate in MTX group [ITT]	12_1_8f.RTF
12.1	Listing of the reasons of Methotrexate dose reductions [ITT]	12_1_8g.RTF
12.1	Methotrexate cancellations and reasons [ITT]	12_1_9a.RTF
12.1	Listing of the reasons of Methotrexate cancellations [ITT]	12_1_9b.RTF
12.1	Vinflunine cancellations and reasons [ITT]	12_1_9c.RTF
12.1	Listing of the reasons of Vinflunine cancellations [ITT]	12_1_9d.RTF
12.1	Treatment interruption and reasons [ITT]	12_1_10a.RTF
12.1	Listing of the reasons of treatment interruptions [ITT]	12_1_10b.RTF
12.1	Dose discontinuations of Vinflunine or Methotrexate [ITT]	12_1_11a.RTF
12.1	Listing of patients with discontinuation of VInflunine or Methotrexate [ITT]	12_1_11b.RTF
12.2.1	Summary of Adverse Events [Safety set]	12_2_1.RTF

SECTION	Title	RTF reference
12.2.2	Adverse events whatever their relationship to study drug – Worst grade events per patient by SOC and PT [Safety set]	12_2_2_1a.RTF
12.2.2	Adverse events whatever their relationship to study drug – Worst grade events per cycle by SOC and PT [Safety set]	12_2_2_1b.RTF
12.2.2	Drug-related adverse events – Worst grade events per patient by SOC and PT [Safety set]	12_2_2_1c.RTF
12.2.2	Drug-related adverse events – Worst grade events per cycle by SOC and PT [Safety set]	12_2_2_1d.RTF
12.2.2	AEOSI whatever their relationship to study drug – Worst grade events per patient by type [Safety set]	12_2_2_2a.RTF
12.2.2	AEOSI whatever their relationship to study drug – Worst grade events per type [Safety set]	12_2_2_2b.RTF
12.2.2	Drug-related AEOSI – Worst grade events per patient by type [Safety set]	12_2_2_2c.RTF
12.2.2	Drug-related AEOSI – Worst grade events per cycle by type [Safety set]	12_2_2_2d.RTF
12.2.2	Serious adverse events whatever their relationship to study drug – Worst grade events per patient by SOC and PT [Safety set]	12_2_2_3a.RTF
12.2.2	Drug-related Serious adverse events – Worst grade events per patient by SOC and PT [Safety set]	12_2_2_3b.RTF
12.2.2.4	Worst CTCAE grade of haematological parameters by patient [Safety set]	12_2_2_4_1a.RTF
12.2.2.4	Worst CTCAE grade of haematological parameters by cycle [Safety set]	12_2_2_4_1b.RTF
12.2.2.4	Shift table of Worst CTCAE grade by patient according to grade at baseline for haematological parameters [Safety set]	12_2_2_4_1c.RTF
12.2.2.4	Worst CTCAE grade of biochemical parameters by patient [Safety set]	12_2_2_4_2a.RTF
12.2.2.4	Worst CTCAE grade of biochemical parameters by cycle [Safety set]	12_2_2_4_2b.RTF
12.2.2.4	Shift table of Worst CTCAE grade by patient according to grade at baseline for biochemical parameters [Safety set]	12_2_2_4_2c.RTF
12.2.2.4	Worst CTCAE grade of SGOT/AST by patient according to the presence of liver metastases at baseline [Safety set]	12_2_2_4_2d.RTF
12.2.2.4	Worst CTCAE grade of SGPT/ALT by patient according to the presence of liver metastases at baseline [Safety set]	12_2_2_4_2e.RTF
12.2.2.4	Worst CTCAE grade of alkaline phosphatase by patient according to the presence of liver and/or bone metastases at baseline [Safety set]	12_2_2_4_2f.RTF
12.3.1.1	Summary of deaths [Safety set]	12_3_1_1a.RTF
12.3.1.1	Listing of dead patients within 30 days after last administration, reason of death, relationship to treatment [Safety set]	12_3_1_1b.RTF
12.3.1.1	Listing of dead patients within 30 days more than 30 days after last administration, reason of death, relationship to treatment [Safety set]	12_3_1_1c.RTF
12.3.1.2	Listing of Serious Adverse Events [Safety set]	12_3_1_2.RTF
14.1.1	Prior medications whatever the indication per patient at baseline [ITT]	14_1_1.RTF
14.1.2	Prior medications with a tumour related indication per patient at baseline [ITT]	14_1_2.RTF
14.1.3	Prior medications with a prophylactic indication per patient at baseline [ITT]	14_1_3.RTF
14.1.4	Prior medications with pre-treatment event indication per patient at baseline [ITT]	14_1_4.RTF
14.1.5	Prior medications with medical history indication per patient at baseline [ITT]	14_1_5.RTF
14.1.6	Prior medical history by patient according to MedDRA System Organ Class and Preferred Term [ITT]	14_1_6.RTF
14.1.7	Pre-treatment events by patient according to MedDRA System Organ Class and Preferred Term [ITT]	14_1_7.RTF
14.2	Progression-Free Survival (PFS-months) [ITT]	14_2_1.RTF
14.2	Progression-Free Survival (PFS-months) [ITT]	14_2_1_FIG.RTF
14.2	Objective Response Rate (ORR) [ITT]	14_2_2.RTF
14.2	Disease Control Rate (DCR) [ITT]	14_2_3.RTF

SECTION	Title	RTF reference
14.2	Duration Of Response (months) [ITT]	14_2_4.RTF
14.2	Duration Of Response (months) [ITT]	14_2_4_FIG.RTF
14.2	Duration of Disease Control (months) [ITT]	14_2_5.RTF
14.2	Duration of Disease Control (months) [ITT]	14_2_5_FIG.RTF
14.2	Time to Treatment Failure (months) [ITT]	14_2_6.RTF
14.2	Time to Treatment Failure (months) [ITT]	14_2_6_FIG.RTF
14.2	Time to First Response (months) [ITT]	14_2_7.RTF
14.2	Time to First Response (months) [ITT]	14_2_7_FIG.RTF
14.3	Electrocardiogram: listing of abnormalities at baseline [Safety Set]	14_3_1.RTF
14.3	Electrocardiogram: listing of abnormalities during treatment period [Safety Set]	14_3_2.RTF
14.4.1a	Concomitant medications whatever the indication per patient [ITT]	14_4_1a.RTF
14.4.1b	Concomitant medications whatever the indication per cycle [ITT]	14_4_1b.RTF
14.4.2a	Concomitant medications with a tumour related indication per patient [ITT]	14_4_2a.RTF
14.4.2b	Concomitant medications with a tumour related indication per cycle [ITT]	14_4_2b.RTF
14.4.3a	Concomitant medications with a prophylactic indication per patient [ITT]	14_4_3a.RTF
14.4.3b	Concomitant medications with a prophylactic indication per cycle [ITT]	14_4_3b.RTF
14.4.4a	Concomitant medications with pre-treatment event indication per patient [ITT]	14_4_4a.RTF
14.4.4b	Concomitant medications with pre-treatment event indication per cycle [ITT]	14_4_4b.RTF
14.4.5a	Concomitant medications with medical history indication per patient [ITT]	14_4_5a.RTF
14.4.5b	Concomitant medications with medical history indication per cycle [ITT]	14_3_5b.RTF
14.5	EORTC QLQ-C30 (Global Health Status) : Values and changes from baseline Over Time and at last cycle [Evaluable Pop for QLQ-C30]	14_5_1a.RTF
14.5	EORTC QLQ-C30 (Functional scales): Values and changes from baseline Over Time and at last cycle [Evaluable Pop for QLQ-C30]	14_5_1b.RTF
14.5	EORTC QLQ-C30 (Symptom Scales/Items) : Values and changes from baseline Over Time and at last cycle [Evaluable Pop for QLQ-C30]	14_5_1c.RTF
14.5	QLQ-Head and Neck EORTC 35 Module (Multi-item scales) : Values and changes from baseline Over Time and at last cycle [Evaluable Pop for QLQ-H&N 35]	14_5_2a.RTF
14.5	QLQ-Head and Neck EORTC 35 Module (Single items) : Values and changes from baseline Over Time and at last cycle [Evaluable Pop for QLQ-H&N 35]	14_5_2b.RTF
16.2.1	Discontinued patients	16_2_1_1.RTF
16.2.1	Follow-Up data	16_2_1_2.RTF
16.2.2	Protocol Deviations at study entry	16_2_2_1.RTF
16.2.2	Protocol Deviations on treatment	16_2_2_2.RTF
16.2.3	Analysis sets	16_2_3_1.RTF
16.2.3	Eligibility criteria	16_2_3_2.RTF
16.2.3	Randomization criteria	16_2_3_3.RTF
16.2.4	Patients' characteristics	16_2_4_1.RTF
16.2.4	Disease characteristics	16_2_4_2.RTF
16.2.4	Prior surgery for SCCHN	16_2_4_3a.RTF
16.2.4	Prior radiotherapy for SCCHN	16_2_4_3b.RTF
16.2.4	Prior chemotherapy for SCCHN	16_2_4_3c.RTF
16.2.4	Prior treatment for SCCHN	16_2_4_3d.RTF
16.2.4	Medical and Surgical History, Concomitant disease	16_2_4_4.RTF
16.2.4	Pre-treatment events	16_2_4_5.RTF
16.2.4	Blood and Platelet transfusion	16_2_4_6.RTF
16.2.5	Treatment administration of Vinflunine	16_2_5_1.RTF

SECTION	Title	RTF reference
16.2.5	Treatment administration of Methotrexate	16_2_5_2.RTF
16.2.5	Treatment modifications	16_2_5_3.RTF
16.2.5	Cumulative dose, dose intensity and relative dose intensity per arm and per cycle	16_2_5_4.RTF
16.2.6	Tumour assessments	16_2_6_1.RTF
16.2.6	Work-Up	16_2_6_2.RTF
16.2.6	Efficacy parameters (1/2)	16_2_6_3.RTF
16.2.6	Efficacy parameters (2/2)	16_2_6_4.RTF
16.2.7	Adverse Events by patient (Reported Term, Preferred Term and Dates)	16_2_7_1.RTF
16.2.7	Adverse Events by System Organ Class and Preferred Term	16_2_7_2.RTF
16.2.7	Drug-related Adverse Events by patient (Reported Term, Preferred Term and Dates)	16_2_7_3.RTF
16.2.7	Drug-related Adverse Events by System Organ Class and Preferred Term	16_2_7_4.RTF
16.2.7	Serious Adverse Events by patient (Reported Term, Preferred Term and Dates)	16_2_7_5.RTF
16.2.7	Serious Adverse Events by System Organ Class and Preferred Term	16_2_7_6.RTF
16.2.7	Patient deaths	16_2_7_7.RTF
16.2.8	Individual haematological laboratory measurements by patient - grades and values	16_2_8_1.RTF
16.2.8	Individual biochemical laboratory measurements by patient - grades and values	16_2_8_2.RTF
16.2.8	Blood products	16_2_8_3.RTF
16.2.8	Pregnancy test results	16_2_8_4.RTF
16.2.8	Tumour Markers	16_2_8_5.RTF
16.2.9	Temperature, vital signs, weight	16_2_9_1.RTF
16.2.9	Neurological examination, physical examinatioin	16_2_9_2.RTF
16.2.9	ECG results	16_2_9_3.RTF
16.2.10	Prior and Concomitant medications	16_2_10_1.RTF
16.2.10	Concomitant Radiotherapy	16_2_10_2.RTF
16.2.10	Concomitant surgery	16_2_10_3.RTF
16_2_11	EORTC QLQ-C30	16_2_11_1_1.RTF
16_2_11	EORTC QLQ-C30, derived scores	16_2_11_1_2.RTF
16_2_11	QLQ Head & Neck 35 EORTC module	16_2_11_2_1.RTF
16_2_11	QLQ Head & Neck 35 EORTC module, multi-item scales	16_2_11_2_2.RTF

15.2. APPENDIX 2: STATISTICAL ANALYSIS CONVENTIONS

15.2.1. Conventions for calculation of duration

15.2.1.1. Calculation of a duration in monhts or years

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

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

with Date 2 • Date 1.

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

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

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

15.2.1.2. Calculation of a delay or time duration in days

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

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

with Date 2 • Date 1.

15.2.2. Missing data

15.2.2.1. General conventions

Following internal biometry conventions are used:

- "M" stands for an information not present on CRF form,

15.2.2.2.Conventions for dates

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

15.2.2.3.Dose modifications

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

15.2.2.4.overall response of the patient

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

15.2.3. Date of first response and date of progression

15.2.3.1.Date of first response

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

15.2.3.2.Date of progression or death

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

- In the Tumour Assessment Form of the eCRF (during the study or during the follow-up, i.e. after the end of the treatment period),,
- In Death Report Form of the eCRF in case of death without “objective” progression assessed before.

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

15.2.4. Toxicity

15.2.4.1.Haematological toxicities

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

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

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

Calculation of grades will be done using the following boundaries :

Grade	HGB	WBC	PLT	ANC
Grade 0	]20 – 12]	]15 – 4]	]500 – 100]	]10 – 2]
Grade 1	]12 – 10]	]4 – 3]	]100 – 75]	]2 – 1.5]
Grade 2	]10 – 8]	]3 – 2]	]75 – 50]	]1.5 – 1]
Grade 3	]8 – 6.5]	]2 – 1]	]50 – 10]	]1 – 0.5]
Grade 4	< 6.5	< 1	< 10	< 0.5

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

15.2.4.2.Biochemical toxicities

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

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

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

Calculation of grades will be done using the following boundaries :

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

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

15.2.4.3.Definition of a toxic death

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

15.2.4.4.Treatment duration

For arm A, the treatment duration is defined as the time elapsed between the date of 1st administration and the date of the last VFL administration (if MTX not given) + 21 days or the date of the last MTX administration (if given) + 14 days. For arm B, the treatment duration is defined as the time elapsed between the date of the 1st administration and the date of the last D1 administration of the last cycle + 21 days (if D8 and D15 not given) or the date of the last D8 administration of the last cycle + 14 days (if D15 not given) or the date of the last D15 administration of the last cycle + 7 days (if D15 given). Treatment duration will be tabulated by treatment arm, and listed by patient.

15.2.5. End of study

15.2.5.1.Death for progression

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

15.3. APPENDIX 3: ADVERSE EVENTS OF SPECIAL INTEREST

	Adverse Events of Special Interest	**MedDRA (v19.0) Preferred Terms (PT) or High Level Terms (HLT) if specified or graded from laboratory values if specified**
1	**Myelosupression**	neutropenia, leukopenia, anaemia, thrombocytopenia to be graded from haematological lab values
2,1	**Febrile Neutropenia**	
	PT	febrile neutropenia
2,2	**Infections with severe neutropenia (Clinically relevant Infections (potential bacterial origin))**	Time window is defined as 2 days before through 1 day after the onset of an infection during which time grade 3 or 4 neutropenia or grade 4 leukopenia coincides.
	PT	neutropenic infection
	PT	neutropenic sepsis
	PT	abscess limb
	PT	bacteraemia
	PT	bacterial infection
	PT	blood culture positive
	PT	bronchitis bacterial
	PT	cellulitis
	PT	cystitis
	PT	ear infection
	PT	febrile infection
	PT	fungal infection
	PT	gastrointestinal infection
	PT	infection
	PT	lobar pneumonia
	PT	localised infection
	PT	lower respiratory tract infection bacterial
	PT	lower respiratory tract infection
	PT	lung infection
	PT	oral infection
	PT	pneumonia
	PT	pneumonia bacterial
	PT	sepsis

	PT	septic shock
	PT	sinusitis
	PT	sinusitis bacterial
	PT	skin infection
	PT	tooth abscess
	PT	tooth infection
	PT	urinary tract infection
	PT	urosepsis
	PT	catheter related infection
	PT	wound infection
3,1	**Constipation**	
	PT	constipation
3,2	**Ileus**	
	PT	ileus paralytic
	PT	ileus spastic
	PT	ileus
	PT	subileus
	PT	megacolon
3,3	**Intestinal Obstruction**	
	PT	gastrointestinal obstruction
	PT	intestinal obstruction
	PT	small intestinal obstruction
	PT	large intestinal obstruction
	PT	mechanical ileus
	PT	colonic obstruction
	PT	gastrointestinal stenosis
	PT	intestinal stenosis
	PT	colonic stenosis
3,4	**Abdominal Pain**	
	PT	Abdominal pain
	PT	Abdominal pain lower
	PT	abdominal pain upper
	PT	abdominal rebound tenderness

	PT	abdominal tenderness
	PT	gastrointestinal pain
	PT	visceral pain
4,1	**Nausea**	
	PT	Nausea
4,2	**Vomiting**	
	PT	Vomiting
4,3	**Stomatitis/mucositis**	
	PT	aphthous stomatitis
	PT	mouth ulceration
	PT	mucocutaneous ulceration
	PT	mucosal inflammation
	PT	mucosal ulceration
	PT	stomatitis
	PT	stomatitis haemorrhagic
4,4	**Diarrhoea**	
	PT	Diarrhoea
5,1	**Myocardial Infarction/ Ischaemia**	
	PT	acute myocardial infarction
	PT	myocardial infarction
	PT	silent myocardial infarction
	PT	papillary muscle infarction
	PT	acute coronary syndrome
	PT	angina pectoris
	PT	angina unstable
	PT	Prinzmetal angina
	PT	myocardial ischaemia
	PT	ECG signs of myocardial ischaemia
5,2	**Cardiac Arrhythmias**	
	HLT	Rate and rhythm disorders NEC
	HLT	supraventricular arrhythmias
	HLT	Ventricular arrhythmias and cardiac arrest
5,3	**Cardiac Conduction Disorders**	

	HLT	Cardiac Conduction disorders
6,1	**Local Injection/Infusion Site Reactions**	
	HLT	injection and infusion site reactions (minus Infusion Site Extravasation and Injection Site Extravasation)
6,2	**Extravasation**	
	PT	Extravasation
	PT	Infusion site extravasation
	PT	Injection site extravasation
7,1	**Peripheral Sensory Neuropathy**	
	PT	Acute polyneuropathy
	PT	Burning sensation
	PT	Dysaesthesia
	PT	Hyperaesthesia
	PT	Hypoaesthesia
	PT	Neuritis
	PT	Neuropathy Peripheral
	PT	Allodynia
	PT	Pallanaesthesia
	PT	Paraesthesia
	PT	Peripheral sensory neuropathy
	PT	Polyneuropathy
	PT	Toxic neuropathy
7,2	**Peripheral Motor Neuropathy**	
	PT	Neuromuscular toxicity
	PT	Peripheral motor neuropathy
	PT	Peripheral sensorimotor neuropathy
7,3	**Autonomic Neuropathy**	
	PT	autonomic neuropathy
	PT	cardiac autonomic neuropathy
	PT	neurogenic bowel
	PT	impaired gastric emptying
8,1	**Asthenia/fatigue**	
	PT	fatigue

	PT	asthenia
8,2	**Myalgia**	
	PT	Myalgia
9	**Immediate Hypersensitivity**	events must be study drug related and occur on the day of study drug infusion (day 1 or within 24 hours after infusion of vinflunine)
	PT	Allergic oedema
	PT	Anaphylactic reaction
	PT	Anaphylactic shock
	PT	Anaphylactoid reaction
	PT	Anaphylactoid shock
	PT	Angioedema
	PT	Bronchospasm
	PT	Bronchial oedema
	PT	Circulatory collapse
	PT	Circumoral oedema
	PT	Drug hypersensitivity
	PT	Drug eruption
	PT	Epiglottic oedema
	PT	Eyelid oedema
	PT	Face oedema
	PT	Flushing
	PT	Hypersensitivity
	PT	Laryngeal oedema
	PT	Laryngospasm
	PT	Laryngotracheal oedema
	PT	Lip swelling
	PT	Lip oedema
	PT	Pharyngeal oedema
	PT	Pruritus generalised
	PT	Rash pruritic
	PT	Shock
	PT	Type I hypersensitivity
	PT	Urticaria

10	**SIADH**	
	PT	Inappropriate antidiuretic hormone secretion
	PT	blood antidiuretic hormone increased
11	**PRES**	
	HLT	Encephalopathy NOS
12	**Hepatic dysfunction**	use total bilirubin of grade >2 combined with either AST grade >2, ALT grade >2 or alkaline phosphatase grade >2

15.4. APPENDIX 4: ANALYSIS OF TUMOUR LOCATION AT BASELINE

Tumour Location at Baseline	Visceral Involvement	Groups for detail of organs involved
ABDOMEN	Yes	OTHER
ADIPOSE TISSUE	No	OTHER
ADRENALS	Yes	OTHER
AREA IN THE LARINGECTOMY ZONE	No	OTHER
BONE	No	OTHER
CERVICAL	No	OTHER
CERVICAL MASS	No	OTHER
CERVIX	No	OTHER
CHEST	No	OTHER
COSTAL	No	OTHER
DENSIFICATION INFILTRATIVE APPEARANCE OF CERVICAL FAT PLANES AND CERVI	No	OTHER
FACE	No	OTHER
HYPOPHARYNX	No	HYPOPHARYNX
KIDNEY	Yes	OTHER
LARYNX	No	LARYNX
LEFT SUBMANDIBULAR GLAND	No	SUBMANDIBULAR GLAND
LEFT SUBMANDIBULARIS AREA	No	SUBMANDIBULAR GLAND
LESION UNDER THE CHIN	No	OTHER
LIVER	Yes	OTHER
LUNG	Yes	OTHER
LYMPH NODE(S)	No	LYMPH NODE(S)
MAXILARY SINUS	No	NASAL SINUS
MEDIASTINUM	No	OTHER
MUSCL	No	OTHER
MUSCLE	No	OTHER
NECK	No	NECK SOFT TISSUE
NECK (SOFT TISSUE)	No	NECK SOFT TISSUE
NOSE	No	NASAL SINUS
ORAL CAVITY	No	ORAL CAVITY
OROPHARYNX	No	OROPHARYNX
PARA-PHARYNX	No	PHARYNX
PARANASAL SINUS	No	NASAL SINUS
PARATHYROIDS	Yes	OTHER
PHARYNX	No	PHARYNX
PLEURA	Yes	OTHER
PLEURAL	Yes	OTHER
PLEURAL EFFUSSION	Yes	OTHER
REGION PARAMEDIAN LEFT	No	OTHER
RENAL	Yes	OTHER
RIGHT SUBMANDIBULAR GLAND	No	SUBMANDIBULAR GLAND

SKIN	**No**	**OTHER**
SOFT TISSUE	**No**	**NECK SOFT TISSUE**
SOFT TISSUE SUBMANDIBULAR REGION	**No**	**SUBMANDIBULAR GLAND**
SOFT TISSUE OF THE CHIN RIGHT SIDE	**No**	**NECK SOFT TISSUE**
SOFT TISSUE SUBMANDIBULAR REGION	**No**	**SUBMANDIBULAR GLAND**
SOFT TISSUES OF THE NECK	**No**	**NECK SOFT TISSUE**
SPLEEN	**No**	**OTHER**
SUBCLAVICULAR	**No**	**OTHER**
SUBCUTIS	**No**	**OTHER**
SUBMANDIBULAR GLAND	**No**	**SUBMANDIBULAR GLAND**
SUPRACLAVICULAR	**No**	**OTHER**
THE SOFT TISSUES OF THE NECK	**No**	**NECK SOFT TISSUE**
THORAX WALL	**No**	**OTHER**
VENTRAL SEGMENT	**No**	**OTHER**