APL-B-021-13 (NCT03070964)

A Phase II Study of Plitidepsin in Patients with Relapsed or Refractory Angioimmunoblastic T-cell Lymphoma

STATISTICAL ANALYSIS PLAN

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ABBREVIATIONS AND GLOSSARY

AE(s)	Adverse Event(s)
AITL	Angioimmunoblastic T-cell Lymphoma
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ASCT	Autologous Stem Cell Transplantation
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	Baseline
BMI	Body Mass Index
BSA	Body Surface Area
CI	Confidence Interval
CPK	Creatine Phosphokinase
CPK-MB	Serum CPK Isoenzymes (Found In Cardiac Muscle)
CR	Complete Remission
CRF	Case Report Form
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
DB	Data Base
DF	Degrees of Freedom
DoR	Duration of Response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EPO	Erythropoietin
FDA	Food and Drug Administration
FU	Follow-up
G-CSF	Granulocyte Colony Stimulating Factor
IA	Investigator Assessment
IDMC	Independent Data Monitorin Committe
Ig	Immunoglobulin
IPI	International Prognostic Index
IR	Independent Review
IRC	Independent Review Committee
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical Dictionary for Regulatory Activities
MUGA	Multiple-gated Acquisition Scan
NA	Not Applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not Evaluable
NHL	Non-Hodgkin Lymphoma
NOS	Not Otherwise Specified
ORR	Overall Response Rate
OS	Overall Survival
OS6	Overall Survival at 6 months
OS12	Overall Survival at 12 months
PCTL	Peripheral T-cell Lymphoma
PD	Progressive Disease
PFS	Progression-free Survival
PFS6	Progression-free Survival at 6 months
PFS12	Progression-free Survival at 12 months
PIAI	Prognostic Index for AITL
PIT	Prognostic Index for Peripheral T-cell lymphoma

PK	Pharmacokinetics
PR	Partial Remission
PS	Performance Status
RBC	Red Blood Cell
R/R	Relapsed/Refractory
SAE(s)	Serious Adverse Event(s)
SD	Stable Disease
SOC	System Organ Class
SPD	Sum of the Product of the Diameters
StD	Standard Deviation
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal
v	Version
WBC	White Blood Cells
WHO	World Health Organization
wk	Week

1 STUDY RATIONALE

Angioimmunoblastic T-cell lymphoma (AITL) is the second most common form of peripheral T-cell lymphoma (PTCL), accounting for approximately 20% of PTCLs and 2% of non-Hodgkin lymphomas (NHL). In the United States, the incidence is approximately 0.05 cases per 100,000 person years. The disease is more common in Europe (29% of PTCL cases) than in the United States or Asia.

The clinical course of AITL varies, with occasional spontaneous remissions. Nevertheless, the prognosis of the disease is dismal, with median survival < 3 years, and with 20–30% of long-term survivors. Different clinical risk factors as well as biological parameters have been described as prognostic factors. In a retrospective study of 157 cases of AITL, a multivariate analysis showed the following covariates as adversely associated with prognosis: male gender, anemia and the presence of mediastinal lymphadenopathy.

Other systems such as the International Prognostic Index (IPI) or the prognostic index for peripheral T-cell lymphoma (PIT) were of limited value in this disease. Recently, a risk model for AITL (prognostic index for AITL, PIAI) was designed based on the following adverse covariates: age > 60 years, performance status ≥ 2, extranodal sites > 1, B-symptoms, and platelet count < 150,000/mL. The simplified PIAI had a low-risk group (zero to one factors) with a 5-year survival of 44%, and a high-risk group (two to five factors) with a 5-year survival of 24%.

In phase I studies conducted with plitidepsin, the schedule consisting of 1-hour i.v. infusion given weekly on D1, 8 and 15 q4wk was found to be the most convenient for patients with NHL. An exploratory phase II clinical trial (APL-B-013-02) was conducted to evaluate the efficacy, tolerability and pharmacokinetics of this weekly plitidepsin schedule at a starting dose of 3.2 mg/m^2 in patients with relapsed/refractory (R/R) aggressive NHL. This phase II trial included two cohorts: patients with non-cutaneous PTCL and patients with other aggressive lymphomas. No remissions were found in the cohort of 33 patients with other aggressive lymphomas. However, interesting antitumor activity was observed in 29 evaluable patients from the non-cutaneous PTCL cohort: ORR was 20.7% (95% CI, 8.0–39.7%) and SD rate was 20.7%.

Plitidepsin was well tolerated in this trial. The most common adverse events (AEs) in the non-cutaneous PTCL cohort were nausea, fatigue, vomiting, myalgia, muscle weakness and pyrexia. The most common grade 3/4 hematological abnormalities were lymphopenia, neutropenia, anemia and thrombocytopenia found in 28%, 12%, 10% and 10% of the cases, respectively.

Nine patients with AITL were included in the cohort of 34 non-cutaneous PTCL patients. Of note, ORR in these nine patients was 33.3%, with CR in two patients (22.2%) and PR in one patient (11.1%). Furthermore, SD was reported in other two patients. The median number of previous lines was 2 and the DoR of the three responders was 121, 12 and 4 weeks, respectively. It should be highlighted that the two patients with CR had bone marrow involvement at diagnosis and had previously failed high dose chemotherapy with stem cell transplantation (SCT) support.

In summary, the interesting antitumor activity observed with plitidepsin in non-cutaneous PTCL was mainly found in patients with AITL. Bearing in mind the small number of

agents with meaningful activity in non-cutaneous PTCL and, in particular, the lack of specific agents with reliable and specific activity in AITL, and considering the important signs of activity of plitidepsin in this disease, this phase II clinical trial was designed to evaluate plitidepsin as single-agent treatment for patients with R/R AITL.

The rationale of the exploratory biomarker objectives is related to recent studies exploring the genetic basis of the disease: a study by Odejide and colleagues showed high incidences of gene mutations of TET2, for example, in 85 AITL tissue samples, as well as in DNMT3A, and IDH2: common and frequent mutations that make AITL more comparable to myeloid disorders than other PTCLs and suggest the need to re-evaluate therapeutic strategies.

Several studies have shown that plitidepsin induces apoptosis in a cell type- and dose-dependent manner, and these effects are related to the induction of early oxidative stress, the activation of Rac1 GTPase and the inhibition of protein phosphatases, which in conjunction cause the sustained activation of JNK and p38 MAPK. The final consequence is the triggering of the mitochondrial apoptotic pathway with caspase 9 and caspase 3 activation. Additional effects may be mediated by indirect effects on the cell microenvironment, mainly mediated by antiangiogenic properties and indirect effects on monocyte-derived cells, including follicular dendritic cells.

2 STUDY DESIGN

Prospective, multicenter, phase II clinical trial.

The aim of this clinical trial is to determine the efficacy of plitidepsin in patients with relapsed/refractory AITL. A total of 60 patients will receive plitidepsin. The primary endpoint will be the ORR according to the Lugano classification response criteria per independent central review.

An Independent Review Committee (IRC) consisting of medical specialists (radiologists and hematologists) who are directly involved in the care of patients with AITL but do not take part in this trial as investigators or sub-investigators, will review all efficacy data and will assign the date of objective response or progression/censoring according to their independent evaluation.

Two futility analyses of the primary endpoint (ORR according to Lugano classification response criteria and per IRC) are planned around six months after approximately 25% and 50% of eligible patients (i.e., 15 and 30 patients respectively with AITL confirmed by central pathological review) have been treated. Two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, will mean that the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise, accrual will continue to a total of 60 patients with AITL confirmed by central pathological review. This decision will be taken at the time by an Independent Data Monitoring Committee (IDMC). The IDMC, which will include specialists in PTCL supported by a medical statistician, will review data provided by the Investigators, the IRC efficacy assessments and safety information and will advise whether the study should continue. Recruitment can continue during the review period.

If there are 19 or more responders over the total of 60 patients, the efficacy of plitidepsin will be considered as clinically relevant in AITL patients.

Operational details for the IRC and IDMC will be detailed in the corresponding charters.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary objective

- To evaluate the efficacy of plitidepsin on the basis of overall response rate (ORR) in patients with relapsing/refractory angioimmunoblastic T-cell lymphoma (AITL).

3.2 Secondary objectives

- To evaluate other efficacy endpoints (time-to-event parameters: duration of response [DoR], progression-free survival [PFS], PFS at 6/12 months [PFS6/PFS12], intrapatient PFS/TTP, overall survival [OS] and OS at 6/12 months [OS6/OS12]).
- To evaluate the safety profile of plitidepsin in this patient population.
- To characterize the pharmacokinetics (PK) of plitidepsin.
- To identify biomarkers that may be predictive of plitidepsin activity.

3.3 Endpoints

Primary endpoint:

- Overall response rate (ORR), defined as the percentage of patients with remission, either complete (CR) or partial remission (PR), according to the Lugano classification response criteria per independent central review. An external IRC will assign the objective response and a progression or censoring date for each patient.

Secondary endpoints:

- ORR per investigator.
- CR rate, defined as the percentage of patients with complete remission according to the Lugano classification response criteria per independent central review and investigator assessment.
- Duration of response (DoR), defined as the time from the date when the remission criteria (PR or CR, whichever is first achieved) are fulfilled to the first date when PD, recurrence or death (due to any cause) is documented. Response will be assessed according to the Lugano classification response criteria per independent central review and investigator assessment.
- Progression-free survival (PFS), defined as the time from the date of first drug administration to the date of PD, death (of any cause), or last tumor evaluation; both independent central review and investigator assessment will be used for the determination of PFS.

- Progression-free survival at 6/12 months (PFS6/PFS12), defined as the Kaplan-Meier estimate of the percentage of patients who are progression-free at six/twelve months after first drug administration; both independent central review and investigator assessment will be used for the determination of PFS.
- Intrapatient PFS/TTP, defined as the ratio of PFS achieved with the experimental treatment *versus* the prior last TTP in the R/R setting.
- Overall survival (OS), defined as the time from the date of first dose to the date of death (of any cause) or last patient contact.
- Overall survival at 6/12 months (OS6/OS12), defined as the Kaplan-Meier estimate of the percentage of patients who are live at six/twelve months after first drug administration.
- Treatment safety [AEs, serious adverse events (SAEs) and laboratory abnormalities] graded according to the NCI-CTCAE, v. 4. Dose reductions, skipped doses or dose delays required due to treatment-related AEs, and reasons for treatment discontinuations will be analyzed.
- Pharmacokinetics (PK), samples for PK analysis will be obtained during Cycle 1 exclusively.
- Exploratory biomarker analysis, correlation of efficacy with molecular markers (targets/pathways) related to the mechanism of action of plitidepsin or to the disease.

4 PATIENTS EVALUABILITY CRITERIA

The study population will include patients who have relapsed or refractory AITL confirmed by local pathological assessment. To be included in this study, the patients must meet all inclusion criteria and no exclusion criteria.

4.1 Analysis sets definitions

"All Included Patients" analysis set is defined as all patients who are included in the study (excluding patients who signed informed consent but are classified as screening failures), independent of whether they received the study drug.

"All Treated Patients" analysis set is defined as all included patients who receive at least part of one dose or infusion of plitidepsin.

"Per Protocol Patients" analysis set is defined as all eligible and treated patients with AITL diagnosis confirmed after central pathological review.

"All Evaluable Patients" analysis set is define as all eligible patients with AITL diagnosis confirmed after central pathological review who receive at least two plitidepsin cycles in which at least two complete infusions have been administered and had at least one disease assessment as well as in patients who discontinue treatment without Cycle 3 tumor assessment after at least two plitidepsin infusions due to disease progression (PD) (or death due to PD) or toxicity (or death due to toxicity), defined as "early PD" and "treatment failures" respectively.

"All Responder Patients" analysis set is defined as all patients with CR or PR as overall best response.

4.2 Efficacy populations

The "All Included Patients" analysis set will be used to show demographic and other baseline characteristics.

The "Per Protocol Patients" analysis set will be used for the primary endpoint analysis of ORR by IRC and for the secondary analyses of ORR by investigator assessment, CR rate and PFS analyses, as well as for OS analyses.

The "All Evaluable Patients" and "All Treated Patients" analysis sets will be used for the secondary endpoint analyses of ORR by IRC, ORR by investigator assessment, CR rate and PFS analyses, as well as for OS analyses.

The "All Responder Patients" dataset will be used for the duration of response (DoR) calculation.

4.3 Safety population

The safety analysis is based on the "All Treated Patients" analysis set.

5 SAMPLE CONSIDERATIONS

The primary endpoint for this study is ORR according to the Lugano classification response criteria per independent review in "Per Protocol Patients" population.

A total of 60 patients with AITL confirmed by central pathological review will be treated, 19 or more responders will be needed to get an overall estimate for response rate higher than 30% and its lower limit for the 95% confidence interval greater than 20% (31.7% CI95% 20.3%–45.0% following the binomial distribution).

The type I error (alpha) associated with this one-sided test is 0.025 and the type II error (beta) is 0.1; hence, statistical power is 90%. The null hypothesis (H0) is set at ORR $\leq$ 20% (P0=0.208) versus the alternative hypothesis (H1) at $\geq$ 40% patients (Pa=0.41) having an objective response, the variance of the standardized test is under the null hypothesis.

Two futility analyses of the primary endpoint (ORR according to Lugano classification and per IRC) are planned to reject the alternative hypothesis six months after 25% and 50% of eligible patients have been treated (15 and 30 patients, respectively). Pocock boundary and the actual number of patients confirmed by central pathological review will be used to control type II error for both analyses. For example, if there are two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively. Otherwise,

accrual will continue to a total of 60 patients AITL confirmed by central pathological review. Active recruitment will not be halted while the analysis is being carried out.

Therefore, if there are 19 or more responders of 60 patients, the null hypothesis can be rejected, allowing consideration of the observed activity plitidepsin as clinically relevant in the setting of patients with AITL.

6 STATISTICAL METHODOLOGY FOR EFFICACY

6.1 Planned analyses and definitions

6.1.1 Primary endpoint analysis

Objective response is defined as having partial remission (PR) or better as best overall response based on the the Lugano classification response criteria per independent review. The ***objective response rate (ORR)*** is calculated as the number of objective responders divided by the number of patients in the "Per Protocol Patients" analysis set.

6.1.2 Secondary endpoints analyses

The ***overall response rate (ORR)*** is calculated as the number of objective responders based on the the Lugano classification response criteria per independent review divided by the number of patients in the "All Evaluable Patients" and "All Treated Patients" analysis sets.

The ***overall response rate (ORR)*** is calculated as the number of objective responders based on the investigator criteria divided by the number of patients in the "Per Protocol Patients", "All Evaluable Patients" and "All Treated Patients" analysis sets.

The ***complete remission rate*** is calculated as the number of patients with complete remission based on the the Lugano classification response criteria per independent review or per investigator assessment divided by the number of patients in the "Per Protocol Patients", "All Evaluable Patients" and "All Treated Patients" analysis sets.

The ***duration of response (DoR)*** will be analyzed in the "All Responder Patient". Duration of response will be calculated from the date of first documentation of response to the date of disease progression, recurrence or death with the same censoring rules as PFS. Response will be assessed according to the Lugano classification response criteria per independent central review and investigator assessment.

Progression-free survival (PFS) is defined as the time from the date of first administration to the date of documented progressive disease (PD) or death (regardless of the cause of death). If the patient receives further antitumor therapy (including stem cell transplant) before, PFS will be censored on the date of the last disease assessment prior to the administration of this antitumor therapy. If the patient is lost to follow-up for the assessment of progression the PFS will be censored at the date of last valid tumor assessment. If the patient does not received any drug infusion, he/she will be censored at time zero. Both, independent central review and investigator assessments, will be used for the determination of PFS.

Progression-free survival at 6/12 months (PFS6/PFS12), defined as the Kaplan-Meier estimate of the percentage of patients who are progression-free at six/twelve months after first administration; both independent central review and investigator assessment will be used for the determination of PFS.

Within-patient PFS/TTP, defined as the ratio of the PFS achieved with the experimental treatment versus prior last TTP. Intra-patient PFS/TTP ratio will be categorized and analyzed as a dichotomous variable. Clinical benefit will be defined if a >33% longer PFS/TTP with the experimental treatment *vs.* the TTP with the immediate prior chemotherapy (ratio >1.33) is achieved.

Overall survival (OS), defined as the time from the date of first administration to the date of death (of any cause) or last patient contact.

Overall survival at 6/12 months (OS6/OS12), defined as the Kaplan-Meier estimate of the percentage of patients who are alive at six/twelve months after first administration.

Treatment safety [AEs, serious adverse events (SAEs) and laboratory abnormalities] graded according to the NCI-CTCAE, v. 4. Dose reductions, skipped doses or dose delays required due to treatment-related AEs, and reasons for treatment discontinuations will be analyzed.

6.2 Efficacy analysis methods

6.2.1 Primary endpoint

For the evaluation of the main primary endpoint, ***ORR,*** the ”Per Protocol Patients” population, the data from the Independent Review will be used. Binomial estimates with exact 95% CIs will be calculated for the analysis of response rate. A supportive analysis will be also done in the “All Evaluable Patients” and “All Treated Patients” populations and by investigator assessment as a secondary analysis.

6.2.2 Secondary analyses

Time to event endpoints will be used in an exploratory way.

Binomial estimates with exact 95% CIs will be calculated for the analysis of ***complete remission rate*** in the “Per Protocol Patients”, “All Evaluable Patients” and “All Treated Patients” analysis sets by independent review and investigator assessment.

Duration of response will be analyzed according to the Kaplan-Meier method in “All Responder Patients” analysis set by independent review and investigator assessment.

Time to response id defined as the time, in months, from the date of first drug administration to the first documentation of response method in “All Responder Patients” analysis set by independent review and investigator assessment.

PFS analysis will be performed in “Per Protocol Patients”, “All Evaluable Patients” and “All Treated Patients” analysis sets analysis sets according to the Kaplan-Meier method by independent review and investigator assessment. The concordance between the IRC and investigator evaluation of response and PFS will be shown using counts and percentages.

OS analysis will be performed in "Per Protocol Patients", "All Evaluable Patients" and "All Treated Patients" analysis sets analysis sets according to the Kaplan-Meier.

Univariate evaluation of the influence of different prognostic factors on the main efficacy endpoints will be performed. If appropriate, univariate analyses will include prognostic factors/covariates widely reported and recognized by hematologist such as: sex, age at diagnosis, baseline ECOG, Body Surface Area, Ann arbor, extranodal disease, bone marrow involvement, B symptoms, baseline LDH xULN, bulky lesion, IPI, PIT, PIAI, Relapse or refractory, number of prior lines of treatment, previous SCT or time from last PD before inclusion. Further covariates could be included upon hematologist criteria. . ….

Cox proportional hazard models for PFS and OS, and logistic regression models for ORR will include the prognostic factors specified for the univariate analysis. More relevant and explanatory covariates from the univariate analysis will be included in the multivariate analyses (p-value < 0.10). Prognostic factors with more than 10% missing values will be excluded in the multivariate analyses.

7 STATISTICAL METHODOLOGY FOR SAFETY

Patients are evaluable for general safety if they received any study treatment.

7.1 Toxicity and adverse events

All the adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

The toxicity evaluation will be coded with the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.

As far as all the toxicities are concerned, the NCI-CTCAE grade will be used wherever an NCI-CTCAE grading exists. Otherwise, the severity will be noted. As a convention, the term «Grade» will always be used. Toxicities will be described according to the worst NCI-CTCAE grade or, for toxicities which do not form the subject of NCI-CTCAE classification, according to the worst severity. For "Worst per cycle" calculation purpose, onset and end cycle of each event will be derived.

Summary of overall adverse events will be done by body system and preferred term, by severity (worst toxicity grade) and by relationship to the study drug. Events with unknown relationship will be considered as related events for reporting purposes.

A frequency table will be made for the AEs leading to cycle delay, dose reduction, skipped dose, or withdrawal of study medication. Adverse events with outcome of death will also be presented by relationship to the study drug.

All events entered in Adverse Event form with the onset date before the first drug administration, will be reported as Signs and symptoms. Only those events with start date after/equal the first infusion date will be included in AE tables in Safety section (except those including evolution from baseline).

7.2 Clinical laboratory evaluation

Laboratory results will be classified according to the NCI-CTCAE version 4. All laboratory visits reported as "End of treatment" visit will be mapped to the last cycle visit.

For hematology values: absolute neutrophil count, lymphocyte count, WBC count, platelet count and hemoglobin worst grade per patient and per cycle will be displayed.

Time and duration of anemia, neutropenia and thrombocytopenia in cycles with grade 3-4 abnormality will be tabulated.

Overall cross tabulation will be presented for the worst grade during treatment versus the baseline toxicity grading of anemia, lymphopenia, leukopenia, neutropenia and thrombocytopenia.

The worst grade per patient during treatment and per cycle will be also calculated for the biochemical tests: ALT, AST, Total bilirubin, AP, CPK, creatinine, calcium, potassium, sodium, glucose and albumin.

Time and duration of AST, ALT and CPK increases in cycles with grade 3-4 abnormality will be tabulated.

Overall cross tabulation will be presented for the worst grade during treatment versus the baseline toxicity grading of AST, ALT and CPK increase.

7.3 Vital signs, physical examination, left ventricular ejection fraction (LVEF) and electrocardiogram findings

Tabulation will be made summarizing the performance status, body weight, LVEF and electrocardiogram abnormalities at baseline and during the treatment for each patient.

7.4 Deaths and other Serious Adverse Events

Deaths and other Serious Adverse Events will be tabulated.

8 OTHER ANALYSES

Non-continuous variables will be described in frequency tables using counts and percentages. Continuous variables will be described by median, mean, standard deviation, minimum and maximum.

8.1 Baseline and demographic data

Baseline data such as demographics, disease history, prior therapy, prior relevant history, signs and symptoms, electrocardiogram, LVEF, protein measurements, laboratory values and concomitant medication (ATC-WHO coded) will be described following standard tables detailed in Appendix I. When two or more assessments have been done for the same parameter, the last assessment before or on the first drug administration will be taken into account for the analysis.

8.2 Treatment administration

CRF cycles with a theoretical duration of 4 weeks will be used for this analysis.

Total cumulative dose, time on treatment, dose intensity and relative dose intensity, cycle delay, dose omissions, and dose reductions will be described following standard tables detailed in Appendix I.

Total cumulative dose, expressed in mg/m² is the sum of all the plitidepsin doses from the first cycle until last cycle including the dose received in last cycle.

Patients will be considered to be on-treatment for the duration of their treatment and 30 days following the last treatment dose. If the patient starts any new antitumor therapy outside this clinical trial or dies within 30 days of last treatment dose, the date of administration of this new therapy or the date of death will be considered the date of treatment discontinuation.

However, as a convention, for dose intensity calculation purposes, the duration of the last cycle is considered to be 28 days.

Intended dose intensity is the planned dose per cycle divided by the planned number of weeks by cycle (2.4mg/m^2/wk for plitidepsin).

Absolute dose intensity is the actual cumulative dose divided by the number of weeks of treatment. Relative dose intensity (%) is the ratio of absolute dose intensity divided by the intended dose intensity.

The item «Infusion delayed: yes/no» in the case report form (CRF) will be used to calculate the delay (on day 1 infusion). For cycles considered as delayed by the investigator, the delay will be calculated as:

Delay: Date of current drug administration – Date of previous drug administration – 28.

The first infusion of the first cycle will be excluded from all cycle delay and cycle modification calculations.

8.3 Subsequent therapy

A table summarizing the subsequent therapies received after treatment discontinuation will be shown.

Time to first subsequent therapy or death will be analyzed as a measure of the time from first drug administration to treatment failure that leads to the need of a further treatment regimen.

8.4 Protocol deviations

Analysis of inclusion/exclusion criteria deviations, retreatment restrictions, used concomitant medication and clinically relevant discontinuations will be done as described in Appendix I.

8.5 Pharmacokinetic and biomarkers analyses

These analyses will be detailed in separate documents.

8.6 Imputation of incomplete dates

The dates of certain historical or current clinical activities are key component for statistical analysis. Incomplete date appears when day, month or year is/are missing, and it could be imputed so that variables like time to and duration of certain event can be calculated. If none of day, month and year is available, then the date is missing, no imputation will be done.

Before treatment start date

If day of a date is unknown then the imputed day will be 15, if the month is also unknown then the imputed date will be July 1st. This assumption will be valid if the imputed date is earlier than the treatment start date; otherwise the imputed date will be the first day of the treatment start month.

Between treatment start and end of treatment

All date variables during treatment where information is needed and is not fully available, for example adverse events or concomitant medications, will be subject of imputation by means of SAS programming. If the day of a date is unknown then the imputed day will be 1, if the month and/or year is also unknown then the imputed date will 1/January. This assumption will be valid if the imputed date is earlier than the treatment start date; otherwise, the imputed date will be the treatment start date.

After end of treatment

To ensure the most conservative approach for the main time-to-event variables (i.e. PFS and OS) that can be affected by missing values the following rules will be implemented by means of SAS programming: if the day of a date is unknown then the imputed day will be 1; if the month is also unknown, then the imputed date will be 1/July. This assumption will be valid if the imputed date occurs later than the last drug administration date; otherwise, the imputed date will be the last drug administration date plus 1 day.

8.7 Subgroup analyses

No specific subgroup analysis is planned for efficacy. However, the influence of prognostic factors on the efficacy endpoints will be studied in the multivariate analysis.

No formal statistical allowance will be made for multiple subgroup investigations, but any apparent subgroup interactions will be interpreted appropriately in a cautious way.

Analysis of safety profile by age, gender, race and body mass index (BMI) will be provided as specified in section 12.7.

Handling of multicenter data

Not applicable.

Handling of multiple comparisons

No formal statistical allowance will be made for multiple comparisons, therefore any apparent subgroup analysis will be interpreted appropriately in a cautious way.

8.8 Decimal places and methods for handling missing data

By default, all results will be rounded to one decimal, except in the case where variables are integer; in that case, they will be reported without decimals, for example, age in years, number of sites. For representing p-values four decimals will be selected as default but they could be rounded to fewer decimals if necessary.
Missing values will not be included in the calculation of outputs.

8.9 Interim and group sequential analyses

Two futility analyses of the primary endpoint (ORR according to the Lugano classification response criteria per independent review) are planned to reject the alternative hypothesis when ~25% and ~50% of the patients have been recruited (first 15 and 30 patients, respectively). Pocock boundary and the actual number of patients confirmed by central pathological review will be used to control type II error for both analyses. For example, if there are two or less responders out of 15 patients or seven or less responders out of 30 patients, according to boundaries and sample size assumptions, the alternative hypothesis could be rejected, and thus recruitment might be stopped at the time of the first or second futility analysis, respectively.

8.10 Identification of fixed or random effects models

Not applicable

9 STATISTICAL SOFTWARE

Medidata Rave® EDC will be used for data entry and clinical data management. EAST v5.2 has been used to calculate sample size. SAS v9 (1) or superior will be used for all statistical analysis outputs.

APPENDIX I

All tables will be created at the time of each analysis planned in the protocol if applicable, and at study end.

10 Study Patients

These analyses will be performed in "All Included patients" analysis set.

10.1 Patient disposition

Main characteristics concerning inclusion in the study, withdrawal from the study and protocol deviations will be displayed in this section.

Table 10.1.1 Number of patients per population

	N	%
All Included Patients	X	X.X
All Evaluable Patients		
All Treated Patients		
Per Protocol Patients		

Listing 10.1.2 Patients excluded from analysis populations

Patient id.	Population	Exclusion reason

Table 10.1.3 Patients accrual by institution

	Country	Institution	N	%
No. included	Country 1	Institution 1	X	X.X
		…		
		Total		
	…	Institution 1		
		…		
		Total		
	Total	Institution 1		
		…		
		Total		
No. treated	Country 1	Institution 1		
		…		
		Total		
	…	Institution 1		
		…		
		Total		
	Total	Institution 1		
		…		
		Total		

Table 10.1.4 Study dates

Date of first registration	
Date of first dose of the first patient	
Date of last registration	
Date of first dose of the last patient	
Date of last dose	
Date of last follow-up*	

(*) Last follow-up or exam or procedure before clinical cut-off or study closure

10.2 Reasons for treatment discontinuation

Table 10.2.1 Treatment discontinuation

	N	%
Progressive disease	X	X.X
Treatment related adverse event		
Non treatment related adverse event		
Patient refusal to treatment		
Investigator decision		
Death (due to toxicity)*		
Death (non-treatment-related)**		
Complete response		
PR or CR and eligible for consolidation with autologous or allogeneic SCT		
Other ***		
Total		

(*) Cause of death = study drug related (**) Cause of death = Malignant disease / non study drug related / Other (***) Specify (see listing 10.2.2). Patients included but not treated will not be shown in this table.

When reason for discontinuation is toxicity or study treatment-related death, identify patients and describe them in depth here.

Listing 10.2.2 Reasons for treatment discontinuation other than progressive disease.

Patient id.	Reason	Last cycle	Comments

Listing 10.2.3 Treatment discontinuation due to AEs

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences

Table 10.2.4 Study discontinuation

	N	%
Study termination (clinical cut-off)	X	X.X
Patient's refusal		
Never treated*		
Death (due to toxicity)**		
Death (non-treatment-related)***		
Investigator decision		
Patient's follow-up completed		
Lost to follow-up		
Other ****		
Total		

(*) See Listing 10.2.6 (**) Cause of death = study drug related (***) Cause of death = Malignant disease / non study drug related / Other (****)See Listing 10.2.5

Listing 10.2.5 Study discontinuation due to other reason

Patient id.	Specify

Listing 10.2.6 Patients included but not treated

Patient id.	Off-study reason

Listing 10.2.7 Patients included without AITL diagnosis confirmed after central pathological review

Patient id.	Treated (Y/N)

10.3 Protocol deviations

Listing 10.3.1 Protocol deviations

Patient id.	Deviation type	Description

11 Efficacy Evaluation

11.1 Demographic and other baseline characteristics

These analyses will be performed in "All Included patients" analysis set.

11.1.1 Patient characteristics at baseline

Table 11.1.1.1 Baseline characteristics: Gender

	N	%
Male	X	X.X
Female		
Total		

Table 11.1.1.2 Baseline characteristics: Age at treatment registration

N	Median	Mean	StD	Min	Max

Table 11.1.1.3 Baseline characteristics: Age grouped

	N	%
18-XX	X	X.X
XX-YY		
≥65		
Total		

Table 11.1.1.4 Baseline characteristics: Race

	N	%
White	X	X.X
…		
Total		

11.1.2 Local histopathological diagnosis

Table 11.1.2.1 Histopathological diagnosis: Clinical features

Systemic clinical manifestations	N	%
Generalized lymphadenopathy	X	X.X
Hepatosplenomegaly		
Skin rash/pruritus		
Polyclonal hypergammaglobulinemia		
Others		

Listing 11.1.2.2 Histopathological diagnosis: Clinical features, other clinical manifestations

Patient id.	Other systemic clinical manifestations

Table 11.1.2.3 Histopathological diagnosis: Pathologic and immunophenotypic features

Common T-cell markers (Positive)	N	%
CD3	X	X.X
CD4		
CD8		
Other markers		
Expression of follicular TH (TFH) markers by the tumor cells (Positive)	N	%
PD1	X	X.X
BCL6		
CXCL13		
CD10		
ICOS		
Hyperplasia of follicular dendritic cells (CD23+ and/or CD21+)	N	%
Hyperplasia of follicular dendritic cells (Present)	X	X.X
EBV in-situ hybridization (EBERs) (Positive)		
Presence of CD30+ B-cell blast (Positive)		
Other relevant features		

Listing 11.1.2.4 Histopathological diagnosis: Other common T-cell markers

Patient id.	Other common T-cell markers

Listing 11.1.2.5 Histopathological diagnosis: Other relevant hyperplasia of follicular dentritic cell features

Patient id.	Other relevant features

Listing 11.1.2.6 Patients without AITL diagnosis confirmed by local histopathological report

Patient id.	Reason

11.1.3 Disease at diagnosis, time from diagnosis and current disease

Table 11.1.3.1 Time from diagnosis to first infusion (months)

N	Median	Mean	StD	Min	Max
X	X.X	X.X	X.X	X.X	X.X

Table 11.1.3.2 Time from last PD* to first infusion (weeks)

N	Median	Mean	StD	Min	Max
X	X.X	X.X	X.X	X.X	X.X

(*)PD date will be taken from Lymphoma History form as date of relapsed or refractory disease. If the day or the month or the full date is missing, further information will be taken from Prior anticancer therapy form. After that, if the date is still incomplete, imputation rules described in section 8.6 will be used.

Table 11.1.3.3 Ann-Arbor Lymphoma stage at diagnosis.

	N	%
I-A	X	X.X
I-B		
II-A		
...		
Total		

Table 11.1.3.4 Ann-Arbor Lymphoma stage at diagnosis I/II vs III/IV.

	N	%
I/II	X	X.X
III/IV		
Total		

Table 11.1.3.5 Extranodal disease at diagnosis.

	N	%
Yes	X	X.X
No		
Total		

Listing 11.1.2.6 Extranodal sites at diagnosis.

Patient id.	Extranodal sites

Table 11.1.3.6 Bulky lesion at diagnosis

	N	%
Yes	X	XX.X
No		
Total		

Table 11.1.3.7 International Prognostic Index at diagnosis

	N	%
Low risk (0-1 risk factors)	X	X.X
Low-intermedite risk (2 risk factors)		
High-intermediate risk (3 risk factors)		
High risk (4-5 risk factors)		
Not available		
Total		

Table 11.1.3.8 Prognostic Index for Peripheral T-Cell Lymphoma (PIT) at diagnosis

	N	%
Group 1	X	X.X
Group 2		
Group 3		
Group 4		
Not available		
Total		

Table 11.1.3.9 Prognostic Index for Angioimmunoblastic T-Cell Lymphoma (PIAI) at diagnosis

	N	%
Low risk group	X	X.X
High risk group		
Not available		
Total		

Table 11.1.3.10 Relapsed / Refractory at current disease

	N	%
Relapsed	X	X.X
Refractory		
Total		

Table 11.1.3.11 International Prognostic Index at current disease

	N	%
Low risk (0-1 risk factors)	X	X.X
Low-intermedite risk (2 risk factors)		
High-intermediate risk (3 risk factors)		
High risk (4-5 risk factors)		
Not available		
Total		

Table 11.1.3.12 Prognostic Index for Peripheral T-Cell Lymphoma (PIT) at current disease

	N	%
Group 1	X	X.X
Group 2		
Group 3		
Group 4		
Not available		
Total		

Table 11.1.3.13 Prognostic Index for Angioimmunoblastic T-Cell Lymphoma (PIAI) at current disease

	N	%
Low risk group	X	X.X
High risk group		
Not available		
Total		

Table 11.1.3.14 Baseline characteristics: protein measurements

	N	Median	Mean	StD	Min	Max
Ig G (g/dl)	X	X.X	X.X	X.X	X.X	X.X
Ig A (g/dl)						
Ig M (g/dl)						

Listing 11.1.3.15 Baseline characteristics: protein measurements

Patient id.	Date	Ig G (g/dl)	Ig A (g/dl)	Ig M (g/dl)	Immunofixation serum

11.1.4 Prior anticancer therapy

Listing 11.1.4.1 Patients with prior radiotherapy

Patient id.	Intention	Site (Anatomic)	Total dose (Gy)	First dose	Last dose

Listing 11.1.4.2 Patients with prior surgery

Patient id.	Site and procedures	Date

Table 11.1.4.3 Number of lines of prior medical therapy

	N	%
1	X	X.X
2		
...		
Total		
Median (Range)		

Table 11.1.4.4 Prior anticancer agents

Antineoplastic and Immunomodulating agents (ATC-class.)		
	N	%
Antineoplastic Agents (L01)	X	X.X
….		
….		

Table 11.1.4.5 TTP to last prior anticancer therapy

Time to progression. Last anticancer therapy (months)	N	Median	Mean	StD	Min	Max
Total	X	X.X	X.X	X.X	X.X	X.X

Table 11.1.4.6 Response to last therapy

	N	%
CR	X	X.X
PR		
SD		
PD		
NE / NA / UNK		

Table 11.1.4.7 Prior stem cell transplantation

	N	%
0	X	X.X
1		
≥2		
Type	N	%
Autologous	X	X.X
Allogeneic		

11.1.5 Prior history

Listing 11.1.5.1 Prior history not resolved

Patient id.	Description	Onset Date

11.1.6 Physical examination, vital signs, electrocardiogram and other tests

For the physical examination, vital signs, electrocardiogram and other tests, the last examination available before treatment will be described in the following tables.

Table 11.1.6.1 Baseline characteristics: Physical exam

	N	%
Normal	X	X.X
Abnormal*		
Total		

(*)See listing 11.1.6.2

Listing 11.1.6.2 Physical examination abnormalities

Patient id.	Body system examined	Onset Date

Table 11.1.6.3 Baseline characteristics: Physical exam and vital signs.

Parameter	N	Median	Mean	StD	Min	Max
Weight (kg.)	X	X.X	X.X	X.X	X.X	X.X
Height (cm.)						
BSA (m^2)						
Heart rate (beats/min)						
Systolic blood pressure (mmHg)						
Diastolic blood pressure (mmHg)						
Temperature (ºC)						

Table 11.1.6.4 Baseline characteristics: ECOG Performance Status

	N	%
0	X	X.X
1		
2		
Total		

Table 11.1.6.5 Baseline characteristics: Electrocardiogram

	N	%
Normal	X	X.X
Significant abnormalities*		
Non significant abnormalities		
Total		

(*)See tables of signs and symptoms or prior history for details and listing 11.1.6.6

Listing 11.1.6.6 ECG abnormalities at baseline

Patient id.	Result	Heart rate (bpm)	QT interval (msec)	Fridericia corrected QT (msec)	Specify

Table 11.1.6.7 Baseline characteristics: LVEF

	N	%
Normal	X	X.X
Significant abnormalities*		
Non significant abnormalities*		
Total		

(*)See tables of signs and symptoms or prior history for details and listing 11.1.6.8

Listing 11.1.6.8 Patients with Left Ventricular Ejection Fraction abnormalities at baseline

Patient id.	Date	Result	LVEF (%)	Institutional normal range (%)	Method

Table 11.1.6.9 Baseline characteristics Median and range of LVEF

	N	**Median**	**Mean**	**StD**	**Range**
MUGA	X	X.X	X.X	X.X	X.X-X.X
ECHO					
Both					

Table 11.1.6.10 Baseline characteristics: Neurological examination

	N	%
Normal	X	X.X
Abnormal*		
Total		

(*)See tables of signs and symptoms or prior history for details and listing 11.1.6.11

Listing 11.1.6.11 Neurological examination abnormalities at baseline

Patient id.	Result	Specify

Table 11.1.6.12 Baseline characteristics: Urinary dipstick

	N	%
Normal	X	X.X
Abnormal*		
Total		

(*)See table 11.1.6.13 for further details

Listing 11.1.6.13 Patients with abnormal urinary dipstick at baseline

Patient id.	Date	Result	Proteinuria	Leukocytes	Red Blood Cells

Table 11.1.6.14 Baseline characteristics: Coombs test result

	N	%
Positive	X	X.X
Negative		
Total		

Table 11.1.6.15 Baseline characteristics: Viral serology results

	N	%
Hepatitis B		
Positive	X	X.X
Negative		
Not done		
Total		
Hepatitis C		
Positive	X	X.X
Negative		
Not done		
Total		
Cytomegalovirus		
Positive	X	X.X
Negative		
Not done		
Total		

Listing 11.1.6.16 Patients with positive viral serology results at baseline

Patient id.	Date	Hepatitis B (HBC)			Hepatitis C	Cytomegalovirus	
		Surface antigen	Surface antibody	Core antibody	HCV	CMV pp65	Quantitative CMV DNA PCR

Table 11.1.6.17 Baseline characteristics: Adequate contraception

	N	%
Yes	X	X.X
No		
NA*		
Total		

(*) Specify reasons

Table 11.1.6.18 Baseline characteristics: Pregnancy test

	N	%
Yes	X	X.X
No		
NA*		
Not done		
Total		

(*) Specify reasons

11.1.7 Hematological values at baseline

Table 11.1.7.1 Hematological abnormalities at baseline

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
Leukopenia	X	X	X.X		X	X.X	X	X.X
Anemia								
Thrombocytopenia								
Neutropenia								
Lymphopenia								

(*)Any grade

Table 11.1.7.2 Hematology values at baseline

	N	Median	Mean	StD	Range
WBC (10^9/L)	X	X.X	X.X	X.X	X.X-X.X
Hemoglobin (g/dL)					
Hematocrit (%)					
Platelets (10^9/L)					
Neutrophils (10^9/L)					
Lymphocytes (10^9/L)					

Listing 11.1.7.3 Hematological tests not assessed at baseline

Patient id.	Lab. test

Listing 11.1.7.4 Hematological abnormalities at baseline. Grade ≥ 2

Patient id	Parameter	Value	Grade
		X.X	

11.1.8 Biochemical values at baseline

Table 11.1.8.1 Biochemical abnormalities at baseline

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
AST increase	X	X	X.X		X	X.X	X	X.X
ALT increase								
Total bilirubin increase								
ALP increase								
Creatinine increase								
CPK increase								

(*)Any grade

Table 11.1.8.2 Biochemical values at baseline

	N	Median	Mean	StD	Range
AST (IU/L)	X	X.X	X.X	X.X	X.X-X.X
ALT (IU/L)					
Total bilirubin (mg/dL)					
Direct bilirubin (mg/dL)					
ALP (IU/L)					
Creatinine (mg/dL)					
Creatinine Clearance (ml/min)					
CPK (IU/L)					
CPK MB (IU/L)					
Total proteins (g/dL)					
Albumin (g/dL)					
Uric acid (mg/dL)					
LDH (IU/L)					
CRP (mg/dL)					
Beta-2-microglobulin (mg/L)					

Listing 11.1.8.3 Biochemical tests not assessed at baseline

Patient id.	Lab. test
…	

Listing 11.1.8.4 Biochemical abnormalities at baseline. Grade ≥ 2

Patient id	Parameter	Value	Grade
		X.X	

11.1.9 Other metabolic values at baseline

Table 11.1.9.1 Other metabolic abnormalities at baseline

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
Hyperglycemia	X	X	X.X		X	X.X	X	X.X
Hypoglycemia								
….								
Hypoalbuminemia								

(*)Any grade

Table 11.1.9.2 Other metabolic values at baseline

	N	Median	Mean	Std	Range
Sodium (mmol/L)	X	X.X	X.X	X.X	X.X-X.X
Potassium (mmol/L)					
Calcium (mmol/L)					
Magnesium (mmol/L)					
Glucose (mmol/L)					

Listing 11.1.9.3 Metabolic tests not assessed at baseline

Patient id.	Lab. test
…	

Listing 11.1.9.4 Metabolic abnormalities at baseline. Grade ≥ 2

Patient id	Parameter	Value	Grade
		X,X	

11.1.10 Signs and symptoms at baseline

Table 11.1.10.1 Patients with signs and symptoms at baseline

	N	%
No. signs and symptoms per patient		
0 1 2 ≥ 3	X	X.X
Median (Range)	X.X (X-X)	

Table 11.1.10.2 Signs and symptoms at baseline

		N	Grade 1		…	Grade 4		All*	
SOC	Preferred Term	N	N	%	…	N	%	N	%
		X	X	X.X		X	X.X	X	X.X
Gastrointestinal disorders	Diarrhea NOS								
	…								
General disorders and administration site conditions	Fatigue								
	…								

(*)Any grade

Listing 11.1.10.3 Signs and Symptoms at baseline

Patient id.	Sign/symptom	Grade	Onset date	Relationship	Treated

11.1.11 Concomitant therapy and procedures at baseline

Concomitant medication at baseline according to the ATC classification.

Table 11.1.11.1 Agents of concomitant therapy started at baseline

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Preferred Name	N	%
				X	X.X

Listing 11.1.11.2 Concomitant therapy at baseline

Patient id.	Type	Drug name	ATC Code	Route	Total daily dose	Start date	Reason for use	Indication for therapeutic reason

Listing 11.1.11.3 Concomitant procedures at baseline

Patient id.	Procedure	Date	Indication	AE/MH/Other	Comments

11.2 Measurements of treatment compliance

Not applicable.

11.3 Efficacy analysis

11.3.1 Primary analysis

Table 11.3.1.1 Response rate by the Lugano classification response criteria (Independent Review assessment and "Per Protocol Patients" population)

Response		
	N	%
CR PR SD PD NE	X	X.X

Table 11.3.1.2 Response rate estimates by the Lugano classification response criteria (Independent Review assessment and "Per Protocol Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Response rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.1.3 Response rate by the Lugano classification response criteria (Independent Review assessment and "Per Protocol Patients" population) in first futility analysis

Response	N	%	Pocock boundary
CR PR SD PD NE	X	X.X	

Table 11.3.1.4 Response rate by the Lugano classification response criteria (Independent Review assessment and "Per Protocol Patients" population) in second futility analysis

Response	N	%	Pocock boundary
CR PR SD PD NE	X	X.X	

11.3.2 Secondary analyses

Table 11.3.2.1 Response rate by the Lugano classification response criteria (Investigator assessment and "Per Protocol Patients" population)

Response		
	N	%
CR	X	X.X
PR		
SD		
PD		
NE		

Table 11.3.2.2 Response rate estimates by the Lugano classification response criteria (Investigator assessment and "Per Protocol Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Response rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.3 Response rate by the Lugano classification response criteria (Independent Review assessment and "All Evaluable Patients" population)

Response		
	N	%
CR	X	X.X
PR		
SD		
PD		
NE		

Table 11.3.2.4 Response rate estimates by the Lugano classification response criteria (Independent Review assessment and "All Evaluable Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Response rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.5 Response rate by the Lugano classification response criteria (Investigator assessment and "All Evaluable Patients" population)

Response		
	N	%
CR	X	X.X
PR		
SD		
PD		
NE		

Table 11.3.2.6 Response rate estimates by the Lugano classification response criteria (Investigator assessment and "All Evaluable Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Response rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.7 Response rate by the Lugano classification response criteria (Independent Review assessment and "All Treated Patients" population)

Response		
	N	%
CR	X	X.X
PR		
SD		
PD		
NE		

Table 11.3.2.8 Response rate estimates by the Lugano classification response criteria (Independent Review assessment and "All Treated Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Response rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.9 Response rate by the Lugano classification response criteria (Investigator assessment and "All Treated Patients" population)

Response		
	N	%
CR	X	X.X
PR		
SD		
PD		
NE		

Table 11.3.2.10 Response rate estimates by the Lugano classification response criteria (Investigator assessment and "All Treated Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Response rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.11 ORR – Concordance between Independent Review assessment and Investigator assessment ("Per Protocol Patients" population)

	Response by Investigator assessment				
Response by IRC	CR	PR	SD	PD	NE
CR					
PR					
SD					
PD					
NE					

Table 11.3.2.12 CR rate estimates by the Lugano classification response criteria (Independent Review assessment and "Per Protocol Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
CR rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.13 CR rate estimates by the Lugano classification response criteria (Independent Review assessment and "All Evaluable Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
CR rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.14 CR rate estimates by the Lugano classification response criteria (Independent Review and "All Treated Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
CR rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.15 CR rate estimates by the Lugano classification response criteria (Investigator assessment and "Per Protocol Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
CR rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.16 CR rate estimates by the Lugano classification response criteria (Investigator assessment and "All Evaluable Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
CR rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.17 CR rate estimates by the Lugano classification response criteria (Investigator assessment and "All Treated Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
CR rate	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.18 Duration of response (Independent Review assessment and "All Responder Patients" population)

N	X
Events	X
Censored	X
Median DoR	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.18)

Table 11.3.2.19 Duration of response (Investigator assessment and "All Responder Patients" population)

N	X
Events	X
Censored	X
Median DoR	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.19)

Table 11.3.2.20 Time to response (Independent Review assessment and "All Responder Patients" population)

N	X
Median	X
Minimum	X
Maximum	X.X

Table 11.3.2.21 Time to response (Investigator assessment and “All Responder Patients” population)

N	X
Median	X
Minimum	X
Maximum	X.X

Table 11.3.2.22 PFS (Independent Review assessment and “Per Protocol Patients” population)

N	X
Events	X
Censored	X
Median PFS	X.X
PFS at 6 months	X.X
PFS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.22)

Table 11.3.2.23 PFS (Independent Review assessment and “All Evaluable Patients” population)

N	X
Events	X
Censored	X
Median PFS	X.X
PFS at 6 months	X.X
PFS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.23)

Table 11.3.2.24 PFS (Independent Review assessment and “All Treated Patients” population)

N	X
Events	X
Censored	X
Median PFS	X.X
PFS at 6 months	X.X
PFS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.24)

Table 11.3.2.25 PFS (Investigator assessment and “Per Protocol Patients” population)

N	X
Events	X
Censored	X
Median PFS	X.X
PFS at 6 months	X.X
PFS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.25)

Table 11.3.2.26 PFS (Investigator assessment and “All Evaluable Patients” population)

N	X
Events	X
Censored	X
Median PFS	X.X
PFS at 6 months	X.X
PFS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.26)

Table 11.3.2.27 PFS (Investigator assessment and "All Treated Patients" population)

N	X
Events	X
Censored	X
Median PFS	X.X
PFS at 6 months	X.X
PFS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.27)

Table 11.3.2.28 PFS – Concordance between Independent Review assessment and Investigator assessment ("Per Protocol Patients" population)

	N	%
Event by investigator		
Agreement on event		
Same date		
Later date		
Earlier date		
Censored by investigator		
Agreement on censoring		
Same date		
Different date		
Agreement on status		
Agreement on status and date		

Table 11.3.2.29 Intra-patient PFS/TTP ratio (Independent Review assessment and "Per Protocol Patients" population)

Ratio		
	N	%
≤1.33 >1.33	X	X.X

Table 11.3.2.30 Intra-patient PFS/TTP ratio (Independent Review assessment and "All Evaluable Patients" population)

Ratio		
	N	%
≤1.33 >1.33	X	X.X

Table 11.3.2.31 Intra-patient PFS/TTP ratio (Independent Review assessment and "All Treated Patients" population)

Ratio		
	N	%
≤1.33 >1.33	X	X.X

Table 11.3.2.32 Intra-patient PFS/TTP ratio estimates (Independent Review assessment and "Per Protocol Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Ratio	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.33 Intra-patient PFS/TTP ratio estimates (Independent Review assessment and "All Evaluable Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Ratio	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.34 Intra-patient PFS/TTP ratio estimates (Independent Review assessment and "All Treated Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Ratio	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.35 Intra-patient PFS/TTP ratio (Investigator assessment and "Per Protocol Patients" population)

Ratio		
	N	%
≤1.33 >1.33	X	X.X

Table 11.3.2.36 Intra-patient PFS/TTP ratio (Investigator assessment and "All Evaluable Patients" population)

Ratio		
	N	%
≤1.33 >1.33	X	X.X

Table 11.3.2.37 Intra-patient PFS/TTP ratio (Investigator assessment and "All Treated Patients" population)

Ratio		
	N	%
≤1.33 >1.33	X	X.X

Table 11.3.2.38 Intra-patient PFS/TTP ratio estimates (Investigator assessment and "Per Protocol Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Ratio	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.39 Intra-patient PFS/TTP ratio estimates (Investigator assessment and "All Evaluable Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Ratio	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.40 Intra-patient PFS/TTP ratio estimates (Investigator assessment and "All Treated Patients" population)

	Proportion	Lower 95% limit	Upper 95% limit
Ratio	X.X	X.X	X.X

Binomial exact estimator and 95% confidence interval

Table 11.3.2.41 OS ("Per Protocol Patients" population)

N	X
Events	X
Censored	X
Median OS	X.X
OS at 6 months	X.X
OS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.41).

Table 11.3.2.42 OS ("All Evaluable Patients" population)

N	X
Events	X
Censored	X
Median OS	X.X
OS at 6 months	X.X
OS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.42).

Table 11.3.2.43 OS ("All Treated Patients" population)

N	X
Events	X
Censored	X
Median OS	X.X
OS at 6 months	X.X
OS at 12 months	X.X

Kaplan-Meier plot will be also shown (Figure 11.3.2.43).

11.3.3 Follow-up

Median follow-up assessments will be calculated using the Kaplan-Meier method reversing the censoring values (2). In addition, descriptive median and range will be calculated.

Table 11.3.3.1 Median FU for PFS

	Median	95% CI
Follow-up	X.X	X.X-X.X

Table 11.3.3.2 Descriptive median FU for PFS

	Median	Min	Max
Follow-up	X.X	X.X	X.X

Table 11.3.3.3 Median FU for OS

	Median	95% CI
Follow-up	X.X	X.X-X.X

Table 11.3.3.4 Descriptive median FU for OS

	Median	Min	Max
Follow-up	X.X	X.X	X.X

11.3.4 Multivariate analyses

Table 11.3.4.1 Multivariate analysis of PFS (Independent Review assessment and "Per Protocol Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.2 Multivariate analysis of PFS (Investigator assessment and "Per Protocol Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.3 Multivariate analysis of PFS (Independent Review assessment and "All Evaluable Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.4 Multivariate analysis of PFS (Investigator assessment and "All EvaluablePatients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.5 Multivariate analysis of PFS (Independent Review assessment and "All Treated Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.6 Multivariate analysis of PFS (Investigator assessment and "All Treated Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.7 Multivariate analysis of ORR (Independent Review assessment and "Per Protocol Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.8 Multivariate analysis of ORR (Investigator assessment and "Per Protocol Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.9 Multivariate analysis of ORR (Independent Review assessment and "All Evaluable Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.10 Multivariate analysis of ORR (Investigator assessment and "All Evaluable Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.11 Multivariate analysis of ORR (Independent Review assessment and "All Treated Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.12 Multivariate analysis of ORR (Investigator assessment and "All Treated Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Odds Ratio	95% Odds Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.13 Multivariate analysis of OS ("Per Protocol Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.14 Multivariate analysis of OS ("All Evaluable Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

Table 11.3.4.15 Multivariate analysis of OS ("All Treated Patients" population)

Analysis of Maximum Likelihood Estimates								
Variable Label	Variable values	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	95% Hazard Ratio Confidence Limits
			X.X	X.X	X.X	X.XXXX	X.X	X.X-X.X

List of covariates in section 6.2.2

11.3.5 Best reduction in sum of the product of the diameters lesions

Table 11.3.5.1 Best reduction in sum of product of diameters from baseline

SPD	N	Median	Mean	StD	Min	Max
	X	X.X	X.X	X.X	X.X	X.X

Waterfall plot (Figure 11.3.5.1) will be also shown for all patients with at one disease assessment after treatment.

11.3.6 Characteristics of responders

A summary of the main characteristics of patients showing clinical benefit, defined as patients with PR or better as best response or SD longer than 6 months assessed by Independent Review or by Investigators will be shown.

Listing 11.3.6.1 Characteristics of patients with clinical benefit.

Patient id.	Gender PS Age	Ann-Arbor stage	Bulky Lesion	Relapsed / Refractory	IPI	PAI	PIAI	No. of prior lines	Cycles received	Best response Lugano (IA)	Best response Lugano (IR)	Best PET SUV reduction (%)	PFS (IA)	DR (IA)	PFS (IR)	DR (IR)	OS

IR- Independent review IA- Investigator assessment

12 Safety Analysis

Safety analysis will be carried out on the "All Treated Patients" population.

12.1 Extent of exposure

12.1.1 Treatment administration

Table 12.1.1.1 Number of cycles administered and dose intensity

No. of cycles administered per patient	N	%
1 2 3 …	X	X.X
Median (range)	X.X (X-X)	
Time on treatment (weeks) Median Range	 X.X X.X-X.X	
Plitidepsin cumulative dose (mg/m²) Median Range	 X.X X.X-X.X	
Plitidepsin dose intensity (mg/m²/wk) Median Range	 X.X X.X-X.X	
Plitidepsin relative dose intensity (%) Median Range	 X.X X.X-X.X	

12.1.2 Cycle delays

12.1.2.1 Number of patients and cycles with dosing delay, any relationship

Listing 12.1.2.1.1 Delays

Patient id.	Cycle	Day	Previous cycle	Previous cycle start date	Delayed cycle	Delayed cycle start date	Dose Delay calculated. (days)	Reason for dose delay	Dose Delay Spec.
							X		

Table 12.1.2.1.2 Number of patients and cycles with dosing delay, any relationship

	N	%
No. of patients treated	X	X.X
No. of patients susceptible to have a dosing delay*		
No. of patients with any dose delay**		
No. of cycles administered		
No. of cycles susceptible to be delayed***		
No. of cycles with dosing delay****		
No. of patients with No cycles delayed 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed		

(*) All patients with more than one cycle. (**) Denominator = Number of patients susceptible to have a dosing delay
(***) All cycles excluding first cycle. (****) Denominator= Number of cycles susceptible to be delayed

Table 12.1.2.1.3 Number of patients and cycles with dosing delay according to the relationship

	Treatment-related		Non-treatment-related	
	N	%	N	%
No. of patients with * 1 cycle delayed 2 cycles delayed ≥ 3 cycles delayed	X	X.X		
No. of cycles with dosing delay**				

(*) Denominator = Number of patients susceptible to have a dosing delay (**) Denominator= Number of cycles susceptible to be delayed.

Table 12.1.2.1.4 Length of dosing delay.

		Treatment-related		Non-treatment-related		Total	
Length of delay	Median (range)						
Length of delay		N	%	N	%	N	%
<= 7 days		X	X.X				
>7 days and <=14 days							
> 14 days							

(*) Denominator= Number of cycles susceptible to be delayed.

Listing 12.1.2.1.5 Cycle delays due to AEs

Patient id.	Cycle	Delay reason according to Exposure form	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences

AEs with action = 'Dose delayed' or 'Reduced and delayed'.

12.1.3 Dose omissions

Listing 12.1.3.1 Dose omissions

Patient id.	Cycle	Day	Cycle start date	Reason for dose omission	Dose omission Spec.

Table 12.1.3.2 Number of patients and cycles with dose omitted, any relationship

	N	%
No. of patients treated	X	X.X
No. of patients susceptible to have a dose omission *		
No. of patients with any dose omitted **		
No. of patients with **:		
No plitidepsin omissions		
1 cycle with plitidepsin dose omitted		
2 cycles with plitidepsin dose omitted		
≥ 3 cycles with plitidepsin dose omitted		
No. of cycles administered		
No. of cycles susceptible to have any dose omitted***		
No. of cycles with plitidepsin dosing omitted****		
No. of cycles with plitidepsin dosing omitted (treatment-related)		

(*) All patients with more than one infusion. (**) Denominator = Number of patients susceptible to have a dose omission
(***) All cycles excluding first cycle. (****) Denominator= Number of cycles susceptible to have a dose omission
NA: Not applicable

Table 12.1.3.3 Number of cycles with treatment-related dose omission by patient

	N	%
No. of patients with:	X	X.X
No omission		
1 cycle with treatment-related plitidepsin dose omitted		
2 cycles with treatment-related plitidepsin dose omitted		
≥ 3 cycles with treatment-related plitidepsin dose omitted		

Denominator= Number of patients that were on treatment on day 8 of cycle 1.
NA: Not applicable

Table 12.1.3.4 Reasons for dose omissions

Reasons for omissions	N	%
Treatment-related	X	X.X
Non–treatment-related		

NA: Not applicable

Listing 12.1.3.5 Dose omissions due to AEs

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences

AEs with action = 'Dose skipped" on day 8 or 15.

12.1.4 Dose reductions

All dose reductions should be considered and described, specifying the reason for reduction (drug related, non-drug related or other causes).

Listing 12.1.4.1 Dose reductions

Patient id.	Cycle	Day	Cycle start date	Previous dose	Reduced dose	Reason for dose reduction	Dose reduction Spec.

Table 12.1.4.2 Number of patients and cycles with dose reduction, any relationship

	N	%
No. of patients treated	X	X.X
No. of patients susceptible to have a dose reduced*		
No. of patients with any dose reduced**		
No. of patients with**:		
No plitidepsin reduction		
1 cycle with plitidepsin dose reduced		
2 cycles with plitidepsin dose reduced		
No. of cycles administered		
No. of cycles susceptible to have any dose reduced***		
No. of cycles with plitidepsin dose reduced ****		
No. of cycles with plitidepsin dose reduced (Treatment-related)		

(*) All patients with more than one infusion. (**) Denominator = Number of patients susceptible to have a dose reduced (***) All cycles excluding first cycle of those patients who have only received the first infusion. (****) Denominator= Number of cycles susceptible to have a dose omission
NA: Not applicable

Table 12.1.4.3 Number of patients and cycles with dose reduction according to the relationship

Reasons for reductions	N	%
No. of cycles with dose reductions*		
Treatment-related	X	X.X
Non-treatment-related		

(*) Denominator= Number of cycles susceptible to have a dose omission
NA: Not applicable

Listing 12.1.4.4 Dose reductions due to AEs

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Significant consequences

AEs with action = 'Dose reduced/adjusted' or 'Reduced and delayed'.

12.1.5 Infusions temporarily interrupted

A listing of the patients who had infusions temporarily interrupted with the corresponding reasons will be provided.

Listing 12.1.5.1 Interrupted Infusions listing.

Patient id.	Cycle	Infusion	Interrupted	Reason
			Yes	

12.1.6 Prophylactic medication administration

A listing of the patients who have not received Ondansetron, Diphenhydramine and Ranitidine or equivalents with the corresponding reasons will be reported.

Listing 12.1.6.1 Patients and cycles without prophylactic medication administration

Patient id.	Cycle	Infusion	Prophylactic medication not taken*	Reason
…				

(*) Ondansetron, diphenhydramine or ranitidine.

12.2 Adverse Events (AEs)

12.2.1 Display of adverse events

Table 12.2.1.1 Summary of adverse events.

	N (%)
Patients with at least one AE regardless relationship	X (X.X)
Any treatment-related AE	
Any grade 3/4 AE	
Any grade 3/4 treatment-related AE	
Any SAE in DB	
Any treatment-related SAE	
Any grade 3/4 SAE	
Any grade 3/4 treatment-related SAE	
AEs leading to death	
AEs treatment-related leading to death	
AEs leading to dose delay	
AEs leading to dose reduction	
AEs leading to treatment discontinuation	
AEs treatment-related leading to treatment discontinuation	

Table 12.2.1.2 Evolution of lymphoma-related AEs at baseline

			Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	Fatigue	Grade 0	X	X.X	X	X.X	X	X.X	X	X.X
		Grade 1								
		……								
	Bone Pain	Grade 0								
		Grade 1								
		……								
	Myopathy	Grade 0								
		Grade 1								
		……								
	…….									

Table 12.2.1.3 Treatment-related* adverse events. Worst grade by patient

		Grade 1		…	Grade 4		All**	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) or Uknown relationship (**) Any grade

Table 12.2.1.4 Treatment-related* adverse events. Worst grade by cycle

		Grade 1		…	Grade 4		All**	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) or Uknown relationship (**) Any grade

Table 12.2.1.5 Adverse Events regardless of relationship. Worst grade by patient

		Grade 1		…	Grade 4		All*	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.2.1.6 Adverse Events regardless of relationship. Worst grade by cycle

		Grade 1		…	Grade 4		All*	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Listing 12.2.1.7 Treatment-related* grade 3-4 adverse events. Worst grade by patient

Patient id.	SOC Name	Preferred term	Grade

(*) or Uknown relationship

Listing 12.2.1.8 Treatment-related* grade 3-4 adverse events. Worst grade by cycle

Patient id.	Cycle	SOC Name	Preferred term	Grade

(*) or Uknown relationship

Listing 12.2.1.9 Adverse Events grade 3-4 regardless of relationship. Worst grade by patient

Patient id.	SOC Name	Preferred term	Grade

Listing 12.2.1.10 Adverse Events grade 3-4 regardless of relationship. Worst grade by cycle

Patient id.	Cycle	SOC Name	Preferred term	Grade

At the time of the analysis, if appropriate, grouping of similar or clinically related items will be made.

12.3 Serious Adverse Events and deaths.

12.3.1 Serious Adverse Events

Table 12.3.1.1 Treatment-related* SAEs. Worst grade by patient

		Grade 1		…	Grade 4		All**	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) or Uknown relationship (**) Any grade

Table 12.3.1.2 Treatment-related* SAEs. Worst grade by cycle

		Grade 1		…	Grade 4		All**	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) or Uknown relationship (**) Any grade

Table 12.3.1.3 SAEs regardless of relationship. Worst grade by patient

		Grade 1		…	Grade 4		All*	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Table 12.3.1.4 SAEs regardless of relationship. Worst grade by cycle

		Grade 1		…	Grade 4		All*	
SOC	Preferred Term	N	%	…	N	%	N	%
Blood and lymphatic system disorders	Anemia NOS	X	X.X		X	X.X	X	X.X
	…							
Cardiac disorders	Arrhythmia NOS							
	…							

(*) Any grade

Listing 12.3.1.5 SAEs

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Status	Grade	Relationship	Onset date	Resolved date	Action	Serious Criteria

SAEs narratives will be provided by the pharmacovigilance department.

12.3.2 Deaths

Table 12.3.2.1 Cause of death

Reason*	N	%
Malignant disease	X	X.X
Treatment-related adverse event		
Other		
Total		

(*) Denominator=Number of patients who died

Listing 12.3.2.2 Deaths

Patient id.	Death date	Cause	Comments	Autopsy	Autopsy report available	Number of cycles administered	Last infusion date	Time on treatment*	Time from Last dose**

(*)Time on treatment: defined as last infusion date plus 30 days, or date of death or subsequent therapy (whichever comes first) minus first infusion date. (**)Time from last dose defined as death date minus last infusion date.

Listing 12.3.2.3 Deaths due to AEs

Patient id.	Cycle	Preferred term code	Adverse event reported (verbatim)	Grade	Relationship	Onset date	Resolved date	Action

12.4 Clinical laboratory evaluation

12.4.1 Hematological abnormalities

Hematological toxicities classified according to the NCI-CTCAE will be calculated for all cycles. The worst grade reached by each patient during treatment will be also calculated.

If serious toxicities happen, special follow-up, with descriptives and graphs (boxplots, line plots) will be made to find out the pattern of thrombocytopenia and neutropenia within and between the different cycles.

Table 12.4.1.1 Hematological abnormalities during treatment, worst grade per patient

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
Leukopenia	X	X	X.X		X	X.X	X	X.X
Anemia								
Thrombocytopenia								
Neutropenia								
Lymphopenia								

(*) Any grade

Table 12.4.1.2 Hematological abnormalities during treatment, worst grade per cycle

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
Leukopenia	X	X	X.X		X	X.X	X	X.X
Anemia								
Thrombocytopenia								
Neutropenia								
Lymphopenia								

(*) Any grade

Listing 12.4.1.3 Grade 3-4 hematological abnormalities during treatment. Worst grade per patient

Patient id.	Test	Grade

Listing 12.4.1.4 Grade 3-4 hematological abnormalities during treatment. Worst grade per cycle

Patient id.	Test	Grade

Listing 12.4.1.5 Hematological tests not assessed at any treatment visit per patient

Patient id.	Lab. test

Listing 12.4.1.6 Hematological tests not assessed by patient and cycle

Patient id.	Cycle	Lab. test

Table 12.4.1.7 Platelets and RBC transfusions during the study

		Platelets (Units)		Red Blood Cells (Units)	
		N	(%)	N	(%)
Platelets (Units)	0 transfusions	X	X.X	X	X.X
	1 transfusion				
	…				
	Median (range)				
Red Blood Cells (Units)	0 transfusions				
	1 transfusion				
	…				
	Median (range)				

These tables will be complemented with plots for the median nadir of neutrophils (Figure 12.4.1.8), platelets count (Figure 12.4.1.9) and hemoglobin values (Figure 12.4.1.10) by cycle along the treatment. Furthermore, if appropriate, graphs of the intercycle time course of neutropenia and thrombocytopenia will be provided. Eventually, graphs comparing the time course during the first and second cycle will be created.

12.4.2 Biochemical abnormalities

Grades of liver toxicity and intercycle pattern of creatinine, CPK, bilirubin, transaminases increase and alkaline phosphatase increase during a cycle will be calculated, as it is explained in the corresponding section for hematological toxicities.

Table 12.4.2.1 Biochemical abnormalities during treatment, worst grade per patient

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
AST increase	X	X	X.X		X	X.X	X	X.X
ALT increase								
Total bilirubin increase								
ALP increase								
Creatinine increase								
CPK increase								

(*) Any grade

Table 12.4.2.2 Biochemical abnormalities during treatment, worst grade per cycle

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
AST increase	X	X	X.X		X	X.X	X	X.X
ALT increase								
Total bilirubin increase								
ALP increase								
Creatinine increase								
CPK increase								

(*) Any grade

Listing 12.4.2.3 Grade 3-4 biochemical abnormalities during treatment. Worst grade per patient

Patient id.	Test	Grade

Listing 12.4.2.4 Grade 3-4 biochemical abnormalities during treatment. Worst grade per cycle

Patient id.	Cycle	Test	Grade

Listing 12.4.2.5 Biochemical tests not assessed at any treatment visit by patient

Patient id.	Lab. test

Listing 12.4.2.6 Biochemical tests not assessed by patient and cycle

Patient id.	Cycle	Lab. test

These tables will be complemented with plots for the median peak of ALT (Figure 12.4.2.7), AST (Figure 12.4.2.8) and CPK values (Figure 12.4.2.9) by cycle along the treatment. If appropriate, graphs of the intercycle time course of ALT, AST and CPK will be provided.

12.4.3 Other metabolic parameters

Table 12.4.3.1 Metabolic abnormalities during treatment, worst grade per patient

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
Hyperglycemia	X	X	X.X		X	X.X	X	X.X
Hypoglycemia								
Hypoalbuminemia								
….								

(*) Any grade

Table 12.4.3.2 Metabolic abnormalities during treatment, worst grade per cycle

	N	Grade 1		…	Grade 4		All*	
	N	N	%	…	N	%	N	%
Hyperglycemia	X	X	X.X		X	X.X	X	X.X
Hypoglycemia								
Hypoalbuminemia								
….								

(*) Any grade

Listing 12.4.3.3 Grade 3-4 metabolic abnormalities during treatment. Worst grade by patient

Patient id.	Test	Grade

Listing 12.4.3.4 Grade 3-4 metabolic abnormalities during treatment. Worst grade by cycle

Patient id.	Cycle	Test	Grade

Listing 12.4.3.5 Metabolic tests not assessed at any treatment visit by patient

Patient id.	Lab. test

Listing 12.4.3.6 Metabolic tests not assessed by patient and cycle

Patient id.	Cycle	Lab. test

12.4.4 Laboratory values over time

In this section, grades 3-4 hematological and liver enzyme abnormalities will be displayed according to the cycle in which they occurred.

Table 12.4.4.1 Evolution of hematological abnormalities from baseline, worst case per patient.

			Worst grade per patient						Total	
			0		1		…			
Baseline	Neutropenia	Grade 0								
		Grade 1								
		……								
	Thrombocytopenia	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

Table 12.4.4.2 Evolution of transaminases abnormalities from BL, worst case per patient.

			Worst grade per patient						Total	
			0		1		…			
			N	%	N	%	N	%	N	%
Baseline	AST increase	X	X.X	X	X.X			X	X.X	
		Grade 1								
		……								
	ALT increase	Grade 0								
		Grade 1								
		……								
	….	Grade 0								
		Grade 1								
		……								

Table 12.4.4.3 Grade 3-4 laboratory abnormalities in the first cycle and in all other cycles

Laboratory abnormalities						
	Cycle 1			Cycle>1		
	No. of cycles evaluated	No. of cycles grade 3-4	%	No. of cycles evaluated	No. of cycles grade 3-4	%
Thrombocytopenia	X	X	X.X	X	X	X.X
Neutropenia						
ALP						
Total bilirubin						
AST						
ALT						
CPK						

Table 12.4.4.4 Hemtological time-course pattern

Laboratory abnormalities	Onset day grade 3-4	Days in grade 3-4	Day of recovery to grade 2			Days to recovery		
			<=28	29-35	>35	<=28	29-35	>35
Anemia	X (X-X)	X (X-X)	X (X.X%)	X (X.X%)	X (X.X%)	X (X.X%)	X (X.X%)	X (X.X%)
Neutropenia								
Thrombocytopenia								

Table 12.4.4.5 ALT/AST/CPK time-course pattern

Laboratory abnormalities	Onset day grade 3-4	Days in grade 3-4	Day of recovery to 2.5 x ULN			Days to recovery		
			<=28	29-35	>35	<=28	29-35	>35
ALT	X (X-X)	X (X-X)	X (X.X%)	X (X.X%)	X (X.X%)	X (X.X%)	X (X.X%)	X (X.X%)
AST								
CPK								

12.5 Vital signs, physical findings, LVEF, ECG and other tests related to safety

12.5.1 Vital signs and physical findings

Table 12.5.1.1 ECOG performance status during the study

	Cycle/PS*						
	0	1	2	3	..	..	..
Patient id.							
…					.	.	.
…					.	.	.

(*) Worst ECOG PS of the cycle determinations.

Table 12.5.1.2 Weight by patient per cycle

	Cycle/Weight						
	0 (kg)	1* (%)	2* (%)	3* (%)	..	..	..
Patient id.							
…	X.X	X.X	X.X	X.X	.	.	.

(*) % of changes respect to baseline

12.5.2 LVEF, ECG and other related tests

Listing 12.5.2.1 Electrocardiogram results. Evolution during the study.

Patient id.	Cycle	ECG result

Listing 12.5.2.2 LVEF evolution during the study.

Patient id.	LVEF(%)		
	Baseline*	Minimun*	End of treatment*
	X.X	X.X	X.X
Median(Range)	X.X (X.X-X.X)	X.X (X.X-X.X)	X.X (X.X-X.X)

(*) LVEF (%) value and method

Listing 12.5.2.3 Median change in LVEF.

Cycles	LVEF
Baseline	X.X (X.X-X.X)
Minimun	X.X (X.X-X.X)
End of treatment	X.X (X.X-X.X)

12.6 Concomitant therapy / procedures according to the ATC classification.

Table 12.6.1 Concomitant medication during treatment (ATC levels)

Medication Term (ATC level 1)	Medication Term (ATC level 2)	Medication Term (ATC level 4)	Preferred Name		
				N	%
				X	X.X

Listing 12.6.2 Patients with EPO or G-CSF.

Patient id.	Type	Route	Dose	Unit	Start date	Stop date	Reason	Indication

Listing 12.6.3 Patients with any transfusion during treatment

Patient	Cycle	Date	Blodd product	Specify	Total units	Irradiated

Taken from concomitant therapy dataset.

Table 12.6.4 G-CSF, transfusions or EPO during treatment

	N	%
G-CSF	X	X.X
Platelets transfusions		
Packed red cells transfusions		
Plasma transfusions		
Cryoprecipitates		
Clotting factors		
EPO		

Table 12.6.5 Subsequent therapy

	N	%
Type Chemotherapy …	X	X.X
Subsequent chemotherapy agents (ATC) … …		

Table 12.6.6 Time to subsequent therapy or death

	Arm A	Arm B	Parameter	p-value
N				
Events				
Censored				
Time to subsequent therapy or death			Log-Rank: HR (95% CI) :	LR: HR:

Kaplan-Meier plot will be also shown (Figure 12.6.7)

12.7 Safety analysis in special subgroups.

Table 12.7.1 Worst grade 3-4 by patient in special subgroups (Gender)

	Male			Female		
	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia	X	X	X.X	X	X	X.X
Neutropenia						
ALP						
Total bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

(*)Any treatment-related toxicity present in >=5% of patients in any group

Table 12.7.2 Worst grade 3-4 by patient in special subgroups (Race)

	White			Other		
	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia	X	X	X.X	X	X	X.X
Neutropenia						
ALP						
Total bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

(*)Any treatment-related toxicity present in >=5% of patients in any group

Table 12.7.3 Worst grade 3-4 by patient in special subgroups (Age)

	<65 years old			≥65 years old		
	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia	X	X	X.X	X	X	X.X
Neutropenia						
ALP						
Total bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

(*)Any treatment-related toxicity present in >=5% of patients in any group

Table 12.7.4 Worst grade 3-4 by patient in special subgroups (BMI)

	<30			≥30		
	N	Grade 3-4	%	N	Grade 3-4	%
Thrombocytopenia	X	X	X.X	X	X	X.X
Neutropenia						
ALP						
Total bilirubin						
AST						
ALT						
CPK						
Nausea						
Vomiting						
Fatigue						
Other*						

(*)Any treatment-related toxicity present in >=5% of patients in any group

APPENDIX II

13 DB Listings

CRF Listings.

-Listing 13.1.1: Screening
-Listing 13.1.2: Demography
-Listing 13.1.3: Contraception and pregnancy test
-Listing 13.1.4: Medical history
-Listing 13.1.5: Lymphoma history
-Listing 13.1.6: Prior radiotherapy
-Listing 13.1.7: Prior surgery
-Listing 13.1.8: Prior anticancer therapy
-Listing 13.1.9: Prophylactic medication
-Listing 13.1.10: Drug administration
-Listing 13.1.11: Hematology laboratory values
-Listing 13.1.12: Coagulation laboratory values
-Listing 13.1.13: Biochemical laboratory values
-Listing 13.1.14: Other metabolic laboratory values
-Listing 13.1.15: Urinary dipstick
-Listing 13.1.16: Viral serology
-Listing 13.1.17: Coombs Test
-Listing 13.1.18: Protein measurements
-Listing 13.1.19: Physical examination
-Listing 13.1.20: Performance status
-Listing 13.1.21: Neurological examination
-Listing 13.1.22: Vital signs
-Listing 13.1.23: Electrocardiogram
-Listing 13.1.24: LVEF
-Listing 13.1.25: Bone marrow assessment
-Listing 13.1.26: Blood product use
-Listing 13.1.27: Adverse events (including signs and symptoms)
-Listing 13.1.28: Concomitant medications
-Listing 13.1.29: Concomitant procedures
-Listing 13.1.30: Other tests/procedures
-Listing 13.1.31: Tumor evaluation
-Listing 13.1.32: Overall response assessment by cycle
-Listing 13.1.33: Best overall response
-Listing 13.1.34: End of treatment
-Listing 13.1.35: Follow up
-Listing 13.1.36: Medical treatment (after end of treatment)
-Listing 13.1.37: Surgery procedures (after end of treatment)
-Listing 13.1.38: Radiotherapy (after end of treatment)
-Listing 13.1.39: Death report form
-Listing 13.1.40: Off study

APPENDIX II

14 Section 16.2 ICH Listings

-ICH Listing 16.2.1: Discontinued patients
-ICH Listing 16.2.2: Protocol deviations
-ICH Listing 16.2.3: Patients excluded from the efficacy analysis
-ICH Listing 16.2.4: Demographic data
-ICH Listing 16.2.5: Compliance and-or Drug Concentration Data
-ICH Listing 16.2.6: Individual Efficacy Response data
-ICH Listing 16.2.7: Adverse Events
-ICH Listing 16.2.8: Individual laboratory measurements

15 References

1. SAS OnlineDoc, V9.
2. Parmar M. Machin D. Survival analysis. A practical approach. Wiley, Chichester, 1995.