ANALYSIS DISPLAY PLAN
ALGORITHMS

Compound:	PHA-848125AC
Protocol No.:	CDKO-125a-006
Protocol title:	Phase II Study of Oral PHA-848125AC in Patients with Thymic Carcinoma Previously Treated with Chemotherapy
Clinical phase:	Phase II
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ALGORITHMS

PATIENT POPULATIONS

Registered /Screened Patients

Patients with at least one information in any section of the CRF, except the one of laboratory normal range.

Screening Failure (Y/N)

Y: if the pt no. begins with 'S' (screening failure)
N: else. (enrolled patient)

Enrolled Patients (Y/N)

The information is collected on the enrollment form.
N: if the pt no. begins with 'S' (screening failure)
Y: else. (enrolled patient)

Treated Patients

All recorded patients with at least one administration of study treatment (i.e. administered dose (mg) > 0 in at least one cycle).

Not Treated Patients

As per difference between Enrolled and Treated Patients.

Evaluable Patients for Efficacy Analysis and Reasons for Non- Evaluability

A patient is considered evaluable for the efficacy analysis in compliance with the protocol if:

1. at least two out of three histological confirmation of thymic carcinoma were received by and Independent Reviewer Committee (see "Demography and Baseline" Section) **(evaluability criterion 1)**
2. the patient received at least 80% of the intended dose for the first two treatment cycles **(evaluability criterion 2)**
3. a baseline tumor/oncologic assessment was performed **(evaluability criterion 3)**
4. at least one on treatment oncologic assessment was performed **(evaluability criterion 4.1) OR** the patient died before the first scheduled oncologic assessment (6 weeks after treatment start **(evaluability criterion 4.2)**

Note: evaluability criterion 2: (Administered dose (mg) $_{(Cycle1+ Cycle2)}$ * 100) / Intended Dose (mg) $_{(Cycle1+ Cycle2)}$) $\geq$ 80% (see "Treatment Administration" Section).

Therefore a variable indicating patient's evaluability will be derived as "Yes" if:

evaluability criterion 1 AND evaluability criterion 2 AND evaluability criterion 3 AND evaluability criterion 4.1 are met
OR
evaluability criterion 1 AND evaluability criterion 2 AND evaluability criterion 3 AND evaluability criterion 4.2 are met

Else, patient's evaluability will be derived as "No".

Accordingly, reasons for non-evaluability will be derived as:
R1 if evaluability criterion 1 is violated
R2 if evaluability criterion 2 is violated
R3 if evaluability criterion 3 is violated
R4 if evaluability criterion 4.1 AND evaluability criterion 4.2 are both violated otherwise R4.1 or R4.2 depending of sub criterion violated.

More than one reason for non evaluability may exist

Age/Sex/Race

This variable is derived by concatenating Age (years) and the first character of the variables Sex and Race.

PATIENT DISPOSITION

Patient Status on Treatment

Patient Status on Treatment is to be classified as the following:

- **Not treated**: Not treated as defined above in patient population section.
- **Still On treatment (Still on Tr.)**: Treated patients as defined above in the patient population section AND
  no Off Treatment Reason Form AND
  no End of AE Reporting Period Form filled in AND
  no Follow-up visit AND
  no Off Study Reason Form AND
  patient died = No (see algorithm on the adverse event section).
- **Off treatment (Off Tr.)**: Treated patients as defined above in the patient population section AND
  Off Treatment Reason Form present OR
  End of AE Reporting Period Form filled in OR
  Follow-up visit OR
  Off Study Reason Form present OR
  patient died = Yes (see algorithm on the adverse event section)

A control listing may be built with all variables needed to implement the algorithm.

Off Treatment Reason not Provided

Classify and report the patient as 'Reason Not Provided' if the patient's status is Off Treatment and one of the following two situations occurs:

1 The Off Treatment Reason Form is available but the reason is missing

OR

2 the Off Treatment Reason Form is not in the DB.

Duration of Treatment

Treatment Duration (weeks) = (<Derived date of the end of treatment> - <Study treatment start date>) / 7
For derivation of the Date of the End of Treatment see corresponding section under Treatment Administration section

Patient Status on FU

Patient Status on FU is to be defined only for 'Off Treatment Patients' (see definition above) as follows:
No FU: No follow up visits

Still on FU (On FU): At least one follow up visit AND
no lost to FU information in survival FU status form AND
no lost to follow up recorded in Off Treatment Reason form AND
no Off Study Reason AND
patient died=No (see algorithm on the adverse event section)

Off FU (Off FU): At least one follow up visit AND
lost to FU information in survival FU status form OR
Off Study Reason OR
patient died = Yes (see algorithm on the adverse event section))

Note: A control listing may be built with all variables needed to implement the algorithm.

Patient Status on Study

Patient Status on Study is to be classified as the following:

- **Still On Study (On)**: no off study reason AND
  pt died = 'N'
- **Off Study (Off)**: off study reason present OR
  pt died = 'Y'

Note: A control listing may be built with all variables needed to implement the algorithm.

Last Recorded Date

Is the date of death for dead patients or the date when the patient was lastly reported alive for the patients with no death reported. The latter date is the latest among the following dates recorded on the CRF:

- "*Last known alive date*" or "*alive as of*" reported in the Follow-up Survival Status Forms;
- Date when Consent was withdrawn by the patient reported in the Off Study Reason Form;
- Date when Investigator's Decision was taken to withdraw patient from study in the Off Study Reason Form;
- Date of 'End of AE Reporting Period' visit in the End of AE Reporting Period Form;
- AEs start and stop dates reported in the Adverse Event Forms, including last AE Follow-up Form, if any;
- Dates of start and stop of concomitant medication reported in the Concomitant Medication Form, if any;
- Dates of start and stop of concomitant radiotherapy reported in the Concomitant Radiotherapy Form, if any;
- Dates of Specimen Collection recorded in the Laboratory Results Forms (any panel);
- Dates of Biopsy in the Biopsy Shipment Form;
- Date(s) of Specimen Collection in the Pharmacokinetics form;
- Dates when Oncologic Assessments reported in the Oncologic Assessment Form were performed, if any, including follow-up;
- Dates of Vital Signs measurements recorded in the Vital Signs Section, log included;
- Last date when study treatment was administered as recorded in the Drug "X" Administration Form;
- Date of Admission and date of Discharge to/from the hospital recorded in the Hospitalization Form;
- Date of CR/PR, either first or confirming scan whichever is the latest, reported in the Best Overall Tumor Response Form;
- Date of PD in Response Status Forms;
- Dates of assessment in the Medical History & Physical Examination Form;
- Dates of Performance Status recorded in the Outcome Measurements Section;
- Dates of ECG assessments recorded in the Electrocardiogram Form;
- Date(s) of Assessment in the CT-Scan /Chest X-ray Form;
- Date(s) of Assessment in the Visual Acuity and Fundoscopic Examination Form whichever is the latest;
- Date(s) of Transfusion in the Blood Derivatives Form;
- Date(s) of Other Antitumor Therapies at Follow-up;

For calculation of the date of death see section "DEATH" below.

Note: A control listing may be built with all variables needed to implement the algorithm.

Last Recorded Date Flag

A flag (§) is to be derived if "Last Recorded Date" is posterior to the "Investigator's Decision" date or the "Consent Withdrawn" date in Off Study form.

Time on Study (days weeks months)

It is the time interval between the Date of Informed Consent and the Last Recorded Date
Last Recorded Date- Informed Consent Date (days)

(Last Recorded Date- Informed Consent Date) / 7 (weeks)
((Last Recorded Date- Informed Consent Date) *12) / 365.25 (months)

Off Study Reason not Provided

If the form Off Study Reason is in the DB and no reason is marked, classify and report the patient as 'Reason Not Provided'.

PROTOCOL DEVIATIONS

Inclusion / Exclusion Criteria ID

In the listings incl. criteria are sequentially numbered as "ICxx" (e.g. IC01); excl. criteria are sequentially numbered as "ECxx" (e.g. EC10).
A few inclusion criteria are reported in the CRF Inclusion / Exclusion criteria pages as 'documented elsewhere on CRF pages' and are derived at the OC DB level in a specific variable.
The answers to Inclusion / Exclusion criteria are typically 'Yes' or 'No'.

Protocol Deviations Flag

All 'No' answers to inclusion criteria (I) or derived inclusion (DI) criteria and all 'Yes' answers to exclusion criteria (E) are to be marked by a *.

DEMOGRAPHY AND BASELINE

Tumor History: Primary Diagnosis, Diagnosis at Study Entry and History of Other Cancer(s)

Derived Date of Primary Diagnosis

If date of primary diagnosis is incomplete, it will to be derived according to the imputation rules defined below:

Derived Date of Primary Diagnosis
- if only day is missing, use day=15 and check the derived date vs. treatment start date. If treatment start date < derived date then use 1 for the missing day.
- if both month and day are missing then compare year of treatment start date and year of diagnosis:
  (a) if year of treatment start date > year of diagnosis then impute 30 June;
  (b) if year of treatment start date = year of diagnosis then impute 01 January.

In the listing, dates are to be reported as they are, i.e. with no day/month imputation.

(Derived) Date of Primary Diagnosis: Weeks/Months to Tr. Start Date and Flag

Weeks to tr. start = (treatment start date) – [derived] date of primary diagnosis) / 7
Months to tr. start = (treatment start date) – [derived] date of primary diagnosis) * 12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings.

Derived Date of Diagnosis at Study Entry

If date of diagnosis at study entry is incomplete, it will to be derived according to the imputation rules defined below:

Derived Date of Diagnosis at Study Entry
- if only day is missing, use day=15 and check the derived date vs. (treatment start date). If (treatment start date) < derived date then use 1 for the missing day.
- if both month and day are missing then stop further computations

In the listing, dates are to be reported as they are, i.e. with no day imputation.

(Derived) Date of Diagnosis at Study Entry: Weeks/Months to Tr. Start Date and Flag

Weeks to tr. start = (treatment start date) – [derived] date of diagnosis at study entry) / 7
Months to tr. start = (treatment start date)– [derived] date of diagnosis at study entry) * 12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings.

Time (weeks/months) from Primary Diagnosis to Diagnosis at Study Entry and Flag

Time (weeks) = ([derived] date of diagnosis at study entry - [derived] date of primary diagnosis) / 7
Time (months) = ([derived] date of diagnosis at study entry - [derived] date of primary diagnosis) * 12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings.

(Derived) Other Cancer (previous): Yes / No; Yes Value Derived and Flag

-- Pts are classified and counted as 'Yes' if: 'Yes' answers to the 'yes/no' initial question (e.g. "Has the pt had previous history…..?") OR at least one detail is reported in the form. Missing or 'No' answers to the 'yes/no' initial question should be changed into 'Yes' (derived Yes).
-- Pts are classified as 'No' if: 'No' answers to the 'yes/no' initial question AND no details are reported in the form.

Derived 'Yes' is to be identified by '*'.

Derived Date of Other Cancer Diagnosis

If date of other cancer diagnosis is incomplete, it will to be derived according to the imputation rules defined below:

Derived Date of Other Cancer Diagnosis
- if only day is missing, use day=15 and check the derived date vs. treatment start date. If (treatment start date) < derived date then use 1 for the missing day.
- if both month and day are missing then compare year of treatment start date and year of diagnosis:

(a) if year of treatment start date > year of diagnosis then impute 30 June;
(b) if year of treatment start date = year of diagnosis then impute 01 January.

In the listing, dates are to be reported as they are, i.e. with no day/month imputation.

(Derived) Date of Other Cancer Diagnosis: Weeks/Months to Tr. Start Date and Flag

Weeks to tr. start = (treatment start date) – [derived] date of other cancer diagnosis) / 7
Months to tr. start = (treatment start date) – [derived] date of other cancer diagnosis) * 12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings.

Tumor History: Independent Review Committee Confirmation

Diagnosis confirmation of thymic carcinoma by the independent review committee is collected on three separate form, one for each reviewer.
Thymic carcinoma diagnosis is confirmed by the reviewer if (s)he ticked either "B3 - Well-differentiated thymic carcinoma" or "C - Thymic carcinoma" as tumor type at diagnosis.

Overall Confirmed Thymic Carcinoma Type at Diagnosis and Flag

For each patient derive the Overall Confirmed Thymic Carcinoma Type as the thymic carcinoma type (see above) indicated by at least two out of the three reviewers. In this case Thymic Carcinoma Confirmed Flag =Y.
If no thymic carcinoma type was indicated by more than one reviewer, thymic carcinoma will not be confirmed and Overall Confirmed Thymic Carcinoma Type is not to be derived. In this case Thymic Carcinoma Confirmed Flag =N.

Tumor History: Prior Antitumor Treatment / Procedures

Prior Antitumor Treatment / Procedures: Yes / No; Yes Value Derived and Flag

- Pts are classified and counted as 'Yes' if:
  'Yes' answers to the 'yes/no' initial question (e.g. "Has the pt had antitumor treatment/procedures……")
  OR
  at least one detail is reported in the form. Missing or 'No' answers to the 'yes/no' initial question should be changed into 'Yes' (derived Yes).
- Pts are classified as 'No' if: 'No' answers to the 'yes/no' initial question AND no details are reported in the form.

Derived 'Yes' is to be identified by '*'.

Derived Prior Antitumor Treatment/Procedures Start and Stop Date

In order to compute time from previous antitumor treatment/procedure, duration of prior antitumor treatment/procedure and time to treatment start it's necessary to derive the prior antitumor treatment/procedure start and stop dates when

one or both are incomplete in the CRF (see Scenario 1)
OR
one (and only one) of them is completely missing in the CRF (see Scenario 2).

Both derived date of prior treatment/procedures start and derived date of prior treatment/procedures stop should be stored in the analysis database.
In the listings, however, dates are to be reported as they are in the CRF.

Scenario 1:
Both prior treatment/procedure start and stop date are recorded in the CRF page for a given Chronological Seq no but one of them is incomplete

If T/P start date is incomplete then:
- if only day is missing, use day = 1 for the missing day.
- if both month and day are missing, then impute 01 January.

If T/P stop date is incomplete then:
- if only day is missing, use day=15 and check the derived T/P stop date vs. treatment start date.
  If treatment start date < derived T/P stop date then use 1 for the missing day.
- if both month and day are missing then compare year of treatment start date and year of T/P stop:
  (a) if year of treatment start date > year of T/P stop then impute 30 June;
  (b) if year of treatment start date = year of T/P stop then impute 01 January.

At the end of the imputation process, verify that the following relation holds:
(derived) T/P start date </= (derived) T/P stop date < treatment start date
If (derived) T/P start date < treatment start date AND (derived) T/P stop date < (derived) T/P start date then:
(derived) T/P stop date = (derived) T/P start date.

If both start and stop date are partially missing stop the derivation process??

Scenario 2:
Only the prior treatment/procedure start date or the prior treatment/procedure stop date is recorded in the CRF page for a given Chronological Seq no.

If the above date is incomplete then:
- if only day is missing, use day=15 and check the derived T/P date vs. treatment start date. If treatment start date < derived T/P date then use 1 for the missing day.
- if both month and day are missing then compare year of treatment start date and year of T/P:
  (a) if year of treatment start date > year of T/P then impute 30 June;
  (b) if year of treatment start date = year of T/P then impute 01 January.

At the end of the imputation process assigned the derived T/P date value both to (derived) T/P stop date and (derived) T/P start date.
If stop date is NA, stop date is set equal to start date for further the purpose of further computations.

Weeks/Months from (Derived) Prior Antitumor Treatment/Procedures Stop Date to Tr. Start Date and Flag

Weeks to tr. start = (treatment start date – [derived] date of prior treatment/procedure stop) / 7
Months to tr. start = (treatment start date – [derived] date of prior treatment/procedure stop) * 12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings.
If, for a given Chronological Seq no., stop date is NA AND start date is a valid date (eg surgeries), then '*' will not be printed in the listings as stop is assumed to be coincident with start date.

Duration (weeks/months) of Prior Antitumor Treatment/Procedures and Flag

Duration (weeks) = ([derived] prior treatment/procedure Stop date - [derived] prior treatment/procedure Start date] / 7
Duration (months) = ([derived] prior treatment/procedure Stop date - [derived] prior treatment/procedure Start date] *12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings (asterisks are not to be reported if either Start Date or Stop Date are NA).

Time (weeks/months) since Previous Antitumor Treatment/Procedures and Flag

Time (weeks) = ([derived] prior treatment/procedure Start date at Current Chron. Seq. No - [derived] prior treatment/procedure Stop date of Previous Chron. Seq. No) / 7
Time (months) = ([derived] prior treatment/procedure Start date at Current Chron. Seq. No - [derived] prior treatment/procedure Stop date of Previous Chron. Seq. No) *12 / 365.25
Estimated times should be identified by a flag variable and by an '*' in the listings. If, for a given Chronological Seq no, stop date is NA AND start date is a valid date (eg surgeries), then '*' will not be printed in the listings as stop is assumed to be coincident with start date.

If both (Derived) Start Date at Current Chronological Sequence No. and (Derived) Stop date at Previous Chron. Sequence No. are incomplete, (Derived) Time since previous Antitumor Treatment will not be calculated because it may be negative-valued.

Prior Antitumor Treatment / Procedures Classification

Each type of therapy recorded on the prior antitumor treatment/procedure CFR will be classified according to the following schema:

Type of therapy	**Classification**
1=Surgery	Surgery
2=Chemotherapy	Systemic therapy
3=Hormone therapy	Systemic therapy
4=Immune therapy	Systemic therapy
5=Local or loco-regional therapy	Systemic therapy
6=Radiation therapy	Radiotherapy
7=Genetic therapy	Systemic therapy
8=Other Physical Treatments	Systemic therapy

9=Sensitizer	Radiotherapy
10=Targeted therapy	Systemic therapy

This classification will allow the matching between the general information of each type of prior antitumor treatment/procedure and the respective details reported in the specific CRF sections (e.g.: details of 'Chemotherapy' will be found in the 'Prior Systemic Therapy' CRF).

Prior Systemic Therapies, Prior Surgeries, Prior Radiotherapies: Yes / No; Yes Value Derived and Flag

To identify whether the patient had any prior systemic therapies, any surgery, any radiotherapies proceed as follows:

Step 1:
(example for Prior Surgery)
Derive Step1_flag_*sur* ='Yes' if 'Yes' answers to the 'yes/no' initial question (e.g. in the case of Surgery: "Was any prior surgery reported in the prior antitumor treatment/procedure form?") OR at least one detail is reported in the form. Missing or 'No' answers to the 'yes/no' initial question should be changed into 'Yes' (derived Yes)
Derive Step1_flag_*sur*='No' if 'No' answers to the 'yes/no' initial question AND no details are reported in the form.
Derived 'Yes' is to be identified by '*'.

Similarly, create the appropriate Step1_flag_*xxx* for each of these sections: Prior Systemic Therapies, Prior Surgeries, Prior Radiotherapies.

Step 2:
(example for Prior Surgery)
derive Step2_flag_*sur* by selecting the 'Prior Antitumor Treatment / Procedures Derived Flag' (see derivation above) when type of therapy is classified as 'Surgery' (see 'Prior Antitumor Treatment/Procedure Classification' schema above)

Similarly, derive the approriate Step2_flag_*xxx* for each type of therapy according to their classification ('Systemic Therapy', 'Surgery', 'Radiotherapy'.

Step 3:
After the derivation of Step1_flag_*xxx* and Step2_flag_*xxx* for each of these topics: Prior Systemic Therapies, Prior Surgeries, Prior Radiotherapies,

- Pts are classified and counted as 'Yes' ('Yes' or derived 'Yes') if Step1_flag_*xxx* = 'Yes' ('Yes' or derived 'Yes') OR Step2_flag_ *xxx* = 'Yes' ('Yes' or derived 'Yes')
- Pts are classified as 'No', else.

Derived 'Yes' is to be identified by '*'.

General Medical History and Physical Examination

Any Relevant Diagnosis: Yes / No; Yes Value Derived and Flag

- Pts are classified and counted as 'Yes' if: 'Yes' answers to the 'yes/no' initial question (e.g. "Has the pt had Any Relevant Medical History?") OR at least one detail is reported in the form. Missing or 'No' answers to the 'yes/no' initial question should be changed into 'Yes' (derived Yes).
- Pts are classified as 'No' if: 'No' answers to the 'yes/no' initial question AND no details are reported in the form.

Derived 'Yes' is to be identified by '*'.

TREATMENT ADMINISTRATION

Treatment and Schedule

Regimen/Schedule
The treatment schedule is "150 mg/day x 7 days q 2 wks"
The per protocol cycle duration in days is 14
The per protocol no. of drug administrations per cycle is 7

Regimen (mg/day)

It is the dose reported on the section 'Patient Enrollment' of the CRF and corresponds to the daily intended dose, i.e. 150 mg/day for 7 days every 14 days.

First Dose Date (Tr. Start Date)

The first date of administration where an administered dose (mg) > 0 is reported is taken as the date of the first study treatment administration

Last Dose Date (Tr. Last Date)

The last date of administration where an administered dose (mg) > 0 is reported is taken as the date of the last study treatment administration

Start Date of a Cycle

It's the date of the first study drug administration within the specific cycle, i.e. when the first administered dose (mg) > 0 is reported.

Total no. of Cycles

For each patient, it's the number of cycles with an administered dose (mg) > 0.

Number of Days of Treatment

For each cycle is the number of days with an administered dose (mg) > 0.

Time on Treatment (days weeks months)

From first dose date to last dose date:

(Last dose date- first dose date)+1 (days)
[(Last dose date- first dose date)+1]/7 (weeks)
[(Last dose date- first dose date)+1] *12 / 365.25 (months)

Derived date of end of treatment

The derivation of the date of end of treatment is necessary to derive both the duration of the last cycle of treatment and the duration of the whole treatment period. For each patient the date of end of treatment will be derived as follows.

1- Compute <derived EOT_1> as the maximum among the following dates:

- date of vital signs and date of performance status assessment in last treatment cycle
- last date of tr. admin in last treatment cycle
- last date of lab. assessment in last treatment cycle (any panel)
- last date of any other assessment (including Visual Acuity and Fundoscopic Examination) in last treatment cycle
- last date of any specimen collection (pharmacokinetics) in last treatment cycle
- date of ecg in last treatment cycle
- date of CT Scan / X ray in last treatment cycle
- date of Physical Examination in last treatment cycle
- (derived) date of per_protocol_end_of_last_cycle as: date of first administration of last cycle + (<per protocol cycle duration> – 1)

2- Compute <derived EOT_2> as the minimum among the following dates:

- Date of death (see sections 'Death')
- End Date of an AE with action taken ='drug permanently withdrawn'
- Consent Withdrawn date in the Off Study Reason form (dataset STST)
- Investigator's decision date in the Off Study Reason form (dataset STST)
- Alive as of date in the Status at Follow-up form
- Last known alive date in the Status at Follow-up
- Other Antitumor Therapies date at Follow-up

3 -Finally compute <Derived date of end of treatment> as the min(<derived EOT_1>, <derived EOT_2>)

Duration of a Cycle (weeks) (Duration for cycle x)

Duration of cycle x (weeks) = (Start date of cycle <'x+1'> - Start date of cycle <x>) / 7
For the last cycle of treatment:

(a) As a general rule: duration of last cycle (weeks) = (Derived date of end of treatment - Start date of the last cycle) / 7
(b) For the purpose of calculating Dose Intensity: duration of last cycle (weeks) = per protocol cycle duration (weeks)

In the listing reporting dose intensity derivations, for the last cycle of treatment, the duration based on the derived end of treatment is to be displayed together with the per protocol cycle duration displayed within brackets.

Treatment Duration (weeks) (for the whole treatment period)

Treatment Duration (weeks) = (Derived date of the end of treatment - Study treatment start date) / 7
For the purpose of calculating Dose Intensity:
Treatment Duration (weeks) = [(Start date of the last cycle + per protocol cycle duration in days) – Study treatment start date] / 7

e.g.: study treatment start date = 01 MAR 2007
start date of the last cycle = 01 JUL 2007
per protocol cycle duration = 2 weeks (i.e. 14 days)
=> treatment duration = (01 JUL 2007 + 14 days) – 01 MAR 2007 = 136 days ~ 19.43 weeks

In the listing reporting dose intensity, the whole treatment duration based on the derived date of end of treatment is to be displayed, together with the per protocol whole treatment duration displayed within brackets.

Intended Dose (mg) (at cycle x)

Intended dose (mg) = Assigned Dose Level (mg/day) * n (where n is the per protocol no. of drug administrations per cycle).

Intended Dose (mg) (whole treatment period)

For each patient the Intended Dose (mg) for the whole treatment period is the sum of all the Intended doses (mg) (at cycle x)

Taken Dose (mg) per Day or Cycle (at cycle x)

Taken dose (mg) per day: as reported for each day on the treatment CRF page.
Taken dose (mg) per cycle: it's the sum of all administered doses per day reported on the CRF for that cycle.

Administered Dose (mg) (whole treatment period)

For each patient the Administered Dose (mg) for the whole treatment period is the sum of all the Administered Doses (mg) (at cycle x).

BSA (m2, calculated) at cycle x

Create a calculated BSA using the following formula:
BSA=Weight in Kg**0.425 * Height in cm**0.725*71.84/10000 (DuBois&DuBois formula)
where weight is the one reported at the cycle on the CRF and height is reported at the pretreatment visit.
If height or weight at cycle is missing, BSA CANNOT BE CALCULATED.

Dose (mg/m2, calculated) per Day or Cycle and Flag

Dose (mg/m2, calculated) = Administered dose (mg) per day or cycle / BSA reported at cycle on the treatment CRF page.

If BSA reported at cycle on the treatment CRF page is missing, use BSA(m2, calculated). If both of them are missing then:

a) at cycles > 1 use BSA of previous cycle: BSA reported on the treatment CRF or, if this is missing, BSA (m2, calculated)
b) at cycle 1 derive the BSA using the weight and height reported at pretreatment using the formula specified above.

Under the circumstances a) or b) Dose (mg/m2 calculated) will have to be flagged and identified in the listings, e.g. by '*'.

% Scheduled Dose

At each cycle:

% Schedule Dose = Administered dose (mg) per Cycle (see above) * 100) / Intended Dose (mg)

Classification of Cycles by Percentage of Scheduled Dose

For the frequency distribution table of cycles by % of scheduled dose the following categories are used:

"Full Dose" when % scheduled dose of the cycle GE 95%
"80% - < Full Dose" when 80% LE % scheduled dose of the cycle LT 95%
"50% - < 80%": when 50% LE % scheduled dose of the cycle LT 80%
"<50%" when % scheduled dose of the cycle LT 50%

Cumulative Dose (mg)

Cumulative Dose (mg) is the cumulative sum of all doses, from start of treatment either up to end of each treatment cycle OR to the end of the treatment, as required by the analysis and the output to be displayed, where dose is defined as:

<Administered Dose (mg) per Cycle>

Absolute Dose Intensity (mg/wk) (at cycle x)

Absolute Dose Intensity (mg/wk) (at cycle x) = Administered Dose (mg) per Cycle (see above) / duration of the cycle in weeks

<duration of the cycle in weeks (see above)> for the last cycle of treatment: the per protocol cycle duration is to be used.

Absolute Dose Intensity (mg/wk) for whole treatment period

Absolute Dose Intensity (mg/wk) (for whole treatment period) = Cumulative Dose (mg) for the whole treatment period (see above) / treatment duration in weeks

<treatment duration in weeks (see above)> = [(Start date of the last cycle + <per protocol cycle duration in days>) – Study treatment start date] / 7

Intended Dose Intensity (mg/wk)

Intended Dose Intensity (mg/wk) = Intended Dose (mg) (see above) / < per protocol cycle duration in weeks >

Relative Dose Intensity (%)

Relative Dose Intensity (%) = Absolute Dose Intensity (mg/wk) / Intended Dose Intensity (mg/wk) * 100.
It may be calculated for a cycle as well as for the whole treatment period.

Treatment Modifications

Treatment modification can occur at the start of each cycle > 1 or within any cycle. Treatment modifications are derived as follows.

At Cycle Start:

"Treatment Delay (Yes/No)" must be derived as 'Yes' if 'Yes' is recorded in the CRF or at least one reason for treatment delay is recorded.
"Dose Reduction (Yes/No)" must be derived as 'Yes' if 'Yes' is recorded in the CRF or at least one reason for dose reduced is recorded.

Within Cycle:

"Intra Cycle Treatment Modification (Yes/No)" must be derived as 'Yes' if 'Yes' is recorded in the CRF or at least one reason for intra-cycle modification is recorded.

"Any Modification (Yes/No)" must be derived as 'Yes' if at least one Treatment Modification <At Cycle Start> and/or <Within Cycle> is recorded or derived.

Reasons for Treatment Modification

For each toxicity class (i.e. hemat./non-hemat./other) the number of patients for whom the analyzed toxicity was reported at least once will be counted regardless of the kind of treatment modification and how many times this kind of toxicity was reported.
If a patient had a treatment modification and no reason was specified at any cycle of treatment, then the patient will be classified as '*Unknown Reason*' in the relevant frequency distribution table.

TREATMENT EFFICACY

Tumor Lesions

Population to be Analyzed

Efficacy listings are to be produced for treated patients, while tables will be produced both for treated and for evaluable patients (see definitions of evaluable patient in the patient population section).

Oncologic Assessment: Time of Assessment

As per protocol, during the treatment period, irrespectively of cycles duration, the first assessments will be performed 6 weeks (between days 42 and 48) after first drug administration, the second one 3 months (between days 92 and 98) after first drug administration, the following ones every 6 weeks (between days 42 and 48) after the previous one (or whenever a clinical deterioration will be observed) and at end of last cycle (if not done in the previous 4 weeks). Patients off-treatment without progressing before the 3rd month oncologic assessment should have been scheduled at the time of endpoint assessment, unless a new antitumor therapy started. In addition regular oncologic assessments of patients withdrawn from study treatment for causes other than disease progression will continue every 6 weeks during follow-up, until PD or until a new antitumor therapy starts. The corresponding information will be collected on the appropriate forms placed outside the treatment cycles.

Lesion Assessment

Premise

Lesions and responses are defined as per RECIST 1.1 criteria

The presence of a lesion is indicated by a lesion number on the CRF. The same lesion number identifies the same lesion throughout the whole study period.

The “individual target lesion” analyses (% change from baseline) will be performed only if the individual target lesion is considered as evaluable, i.e. if the criteria of evaluability for % change described in the algorithm “Individual Target Lesion: Evaluability for % Change” are fulfilled.

The “all target lesions” analyses (sum of measures, % change from baseline, best and worst % Change from baseline, Nadir and %change from Nadir) will be performed only if the set of “all target lesions” is considered as evaluable, i.e. if the criteria of evaluability for % change described in the algorithm “All Target Lesions: Evaluability for % Change” are fulfilled..

Weeks to/from Treatment Start from/to Lesion Assessment Date:

At pre-treatment: (date of lesion assessment – first dose date) / 7
On-Treatment: [(date of lesion assessment – first dose date)] / 7

Lesion Flag for Different Method

For each patient, assessment and lesion, a flag is to be derived if the assessment method for that lesion at the current assessment is different from the method used at the pretreatment (reference assessment).

Individual Target Lesion: Evaluability for % Change

At each assessment after treatment start, a target lesion is considered as 'evaluable' for % change if:

a) The lesion is reported both at pretreatment and at the analyzed visit with the same method and with valid measurements

OR

b) The lesion is a new lesion with valid, non missing method and measurement at the analyzed assessment

Otherwise the lesion will be classified as 'not evaluable' and will not be processed for % change calculation [e.g. the method differs from baseline method, or the lesion is labeled as not assessed, or lesion's measurement is not reported either at the analyzed visit or at baseline].

Individual Target Lesion: %Change from Baseline

At each assessment after treatment start:

- %Change from Baseline = (measure at the current assessment – measure at pretreatment) * 100 / measure at pretreatment.

Notes: % change for new lesions is not to be calculated: they will be taken into account only for % change of all target lesions

All Target Lesions: Evaluability for %Change.

At each assessment after treatment initiation, the set of all target lesions is considered as evaluable for % change if:

a) All lesions assessed at pretreatment are also assessed at the analyzed visit AND

b) There is no lesion at the current assessment which is classified as 'non evaluable' (see above).

All Target Lesions: Sum of Measures

At each assessment (pretreatment included):

- Sum of measures: sum (all target lesions measures).

Note: In the afore described sum, take into account also new target lesions. In the sum of measures take into account also lymph nodes

All Target Lesions: % Change from Baseline

At each assessment after treatment start as:

- %Change from Baseline = (Sum of measures at current assessment – sum of measures at pretreatment)*100 / sum of measures at pretreatment.

All Target Lesions: Nadir (Y/N)

The lowest value of all sums of measures reported throughout the whole study period (baseline included). In the relevant listing a 'Y' is to be put beside the "all target" value corresponding to the nadir value. Only 'Y' values are to be printed.

All Target Lesions: % Change from Nadir

(Current sum of measures – all target lesions nadir value) * 100 / all target lesions nadir value.
It is applicable only for study periods **following** the visit at which the nadir measure is reported.

Tumor Response Status

Assessment Date (calculated)

For each visit when a tumor assessment is performed, derive the assessment date as: min (target and non target lesions assessment dates) among valid dates. In absence of a valid date no date is surrogated.

Weeks from Treatment Start

[(Assessment date (calc.) – first dose date)] / 7.

Date of documented PD and Flags

The date of PD is to be derived as the earliest date-out of the valid ones- among all tumor lesion assessments (non-target lesions included) performed at the (first) assessment when PD was reported in the Response Status form (page 3 of 3 of onc. assessment CRFs). In absence of a valid date no date is surrogated.

Date of PD > start date of the first anti-tumor therapy at follow-up is to be marked with §
A control listing is to be built with all the variables needed to implement the algorithm.

Time (Days, Weeks and Months) to PD

For Overall Response in Study Period:
[(date of documented PD - first dose date)] (days)
[(date of documented PD - first dose date)] / 7 (weeks)
[(date of documented PD - first dose date)] * 12 / 365.25 (months)

Best Overall Response (Confirmed)

It's the best overall tumor response reported on treatment for each patient and collected on the corresponding CRF
In addition to individual response categories recorded on the CRF, for the purpose of table display assign the following categories:
- *Objective response = yes* if patient attained as best response either PR or CR
- *Disease Control = yes* if patient attained as best response either PR or CR or SD

Date of First Response and Flag

For responding patients only
If a patient has a 'CR' or a 'PR' as a best overall tumor response, the date of start of response should be reported (as *date of first onset scan* on the CRF best overall response form). If missing, then it's to be estimated as follows:
max (all tumor lesion assessment dates) at the first tumor assessment visit with an overall response = best overall tumor response.
Estimated dates of first response are to be identified by *.
Note: A control listing is to be built with all the variables needed to implement the algorithm

Date of Confirmed Response and Flag

For responding patients only
If a patient has a 'CR' or a 'PR' as a best overall tumor response, the date of the confirmed response should be reported (as *date of confirming scan* on the CRF best overall response form). If missing, then it's to be estimated as follows:
max (all tumor lesion assessment dates) at the second tumor assessment visit with an overall response = best overall tumor response.
Estimated dates of confirmed response are to be identified by *.
Note: A control listing is to be built with all the variables needed to implement the algorithm.

Best Unconfirmed Tumor Response

It's the 'best' response among all the overall responses reported on the Response Status Forms at each assessment for the patient.
Example: pt X1 has performed three oncologic assessments; on the first assessment the overall response is 'SD', on the second assessment is 'PR', on the third assessment is 'PD', hence the best unconfirmed tumor response will be 'PR'.

Date of Last Oncologic Assessment before PD

It is the Assessment Date (calculated) (see above) of the most recent oncologic assessment with overall tumor response = 'CR' or 'PR' or 'SD'.

Durations

Premise

Duration of response, duration of stable disease and time to progression are to be calculated and saved in DB as days, weeks and months.

Failure/Censored Patients

The patients are classified as failure (*failure = 1*) if:

- they experienced Progressive Disease (independently of the presence of a date of PD) AND (no new anti-tumor therapy is reported at Follow Up OR it is reported with a non valid date)

OR

- date of Progressive Disease ≤ Start Date of first new anti-tumor therapy reported at Follow Up (both dates must be valid)

OR

- they experienced Death with cause "Progressive Disease" or missing (independently of the presence of a date of Death) AND NO new anti-tumor therapy is reported at Follow Up.

Patients will be classified as censored (i.e. *failure* = 0) if they are not failures.

A control listing may be built with all the variables needed to implement the algorithm.

Date of Failure

For failure patients it is the earliest, non missing date between:
1) Date of PD
2) Date of Death with cause "Progressive Disease" or missing
Note that date of failure could be missing.

Date of Censoring

For censored patients:
1) Start date of first new anti-tumor therapy at Follow Up
OR
2) Date of "Last Oncologic Assessment before PD" if no new anti-tumor therapy is reported at Follow Up OR it is reported with a non valid date.
Note that date of censored could be missing.

Response Duration and Censored Patients Flag

For responding patients only
1) For failure patients:
(date of failure – start of response)
2) For censored patients:
(date of censoring - start of response)

For censored patients only: at the end of calculation, if duration of response is missing then set its value to 1.
For failure patients, if date of failure is missing, duration of response won't be computed and will result in a missing value.
In the listing the response duration of censored patients will be identified by a + (e.g. '5 +')

Progression Free Survival (PFS) and PFR at 3 months

Premise

Progression free survival is to be calculated and saved in DB as days, weeks and months.

Failure/Censored Patients

The patients are classified as failure (*failure = 1*) if:

- they experienced Progressive Disease (independently of the presence of a date of PD) AND (no new anti-tumor therapy is reported at Follow Up OR it is reported with a non valid date)

OR

- date of Progressive Disease ≤ Start Date of first new anti-tumor therapy reported at Follow Up

OR

- they died (independently of the presence of a date of Death)

Patients will be classified as censored (i.e. *failure* = 0) if they are not failures.

A control listing may be built with all the variables needed to implement the algorithm.

Date of Failure

For failure patients it is the earliest, non missing date between:

1) Date of PD
2) Date of Death

Note that date of failure could be missing .

Date of Censoring

For censored patients:

- Start date of first new anti-tumor therapy at Follow Up

OR

- Date of "Last Oncologic Assessment" if no new anti-tumor therapy is reported at Follow Up OR it is reported with a non valid date.

Note that date of censoring could be missing .

Progression Free Survival (PFS)

1) For failure patients:
   (date of failure – treatment start date)
2) For censored patients
   (date of censoring - treatment start date)

If at the end of calculation progression free survival is missing, then set its value to 1 regardless of whether the patient is censored or failure.

Progression Free Survival Rate at 3 Months

Per protocol 3rd month assessment should have been performed between 92 and 134 days since treatment start, therefore a patient's status regarding progression free survival at 3 months will be determined according to the following rules:

1) For failure patients

'Success': if 134 ≥ (date of "Last Oncologic Assessment before PD OR before death" – first dose date) ≥ 92.

'Failure': Otherwise

2) For censored patients:

'Success' if: 134 ≥ PFS ≥ 92 days

'Failure': Otherwise

Note. For the purpose of Interim Analysis the primary endpoint PFS rate at 3 months will be evaluated on the first 17 treated and evaluable patients irrespectively they were observed for 3 months or they failed earlier. If 3 or fewer patients out of the first 17 are progression-free at 3 months, the study will stop for futility as soon as this can be determined. If 4 or more patients out of 17 are progression free, the trial will be continued until 54 evaluable patients are available.
The rules to define the patient's status regarding progression free survival at 3 months are the same as reported above in this paragraph.

Overall Survival (OS)

Premise

Overall survival is to be calculated and saved in DB as days, weeks and months.

Failure/Censored Patients

A variable *(failure*) is to be derived to identify failure and censored patients.
1) Patients will be classified as failure (i.e. *failure* = 1) if:
pt died = 'Y'
2) Patients will be classified as censored (i.e. *failure* = 0) if they are not failures.

Overall Survival and Censored Patients Flag

1) For failure patients:
(Death date – study treatment start date)
2) For censored patients:
(Last recorded date – study treatment start date)
If at the end of calculation survival is missing, then set its value to 1 regardless of whether the patient is censored or failure
In the listing overall survival for censored patients will be identified by a + (e.g. '5 +')

Summary Statistics for Time to Events Endpoints: Flag for Censored Patients

For all time to event endpoints (i.e.: progression free survival, overall survival, duration of response).
Derive a flag if the statistics refer to censored patients when calculating MIN and MAX of time to event endpoints,.

ADVERSE EVENTS (AES)

Safety Population

All treated patients. The safety population will be used as the denominator to calculate percentages.

AE terminology criteria: MedDRA and aggregation levels for the analysis

AEs are recorded in the DB as reported in the CRF (Investigator's Term) and coded according to MedDRA (MedDRA Code and Preferred Term). For each MedDRA Preferred Term, the corresponding MedDRA System Organ Class (SOC) is also recorded in the DB.
In the analyses, aggregations both by MedDRA Preferred Term (Aes) and MedDRA System Organ Class (SOC) will be provided.

On treatment Adverse Event

As per protocol all adverse events recorded on treatment (recorded in the AE forms from cycle 1 on, follow-up excluded) will be classified as 'on treatment Aes' and considered in the analysis, regardless of whether they were also recorded as baseline signs and symptoms in the pre-treatment CRF.

Maximum CTC grade by patient and MedDRA Preferred Term

For each patient and for each MedDRA Preferred Term, derive the maximum CTC grade for the on treatment records. In the relevant analyses the patients will be classified according to this derived variable and counted for each MedDRA Preferred Term.

Maximum CTC grade by patient and System Organ Class (SOC)

For each patient and for each system organ class (SOC), derive the maximum CTC grade for the on treatment records. In the relevant analyses the patients will be classified according to this derived variable and counted for each SOC.

Maximum CTC grade by patient

For each patient derive the maximum CTC grade by patient, independently of the event/system, for the on treatment records. In the relevant analyses the patients will be classified according to this derived variable.

Aes: CTC Grade >= 3 Flag

Any ctc grade >/= 3 is to be marked by *.

Aes in Follow-up Flag

Aes not recovered in Follow-up are identified by §.

Deaths

Date of Death

As a general rule the date of death will be defined as:

(1) min (Date of death on CRF Death form, date(s) of death on survival follow-up forms)

If the date of death (1) is not available, it will be derived as

(2) min [Stop date(s) of AE with death as outcome (CRF Adverse Event form)or with CTC grade=5]

Patient Died

Patient died = Yes:

if a death date (see definition above) is not missing
or at least one information on death is reported in death form or in survival follow-up forms
or at least one AE has outcome=death or CTC grade=5.

Patient died = No:

if a death date (see definition above) is missing
and no information on death is reported in death form nor in survival follow-up forms
and no AE with outcome = death nor CTC grade=5.

CRF Source

If death date is obtained from the death form, then CRF Source = '(Death)';
else if death date is obtained from the survival follow-up forms then CRF Source = '(FU)';
else if death date is obtained from the AE forms then CRF Source = '(AE)'.

Days from Last Treatment Administration and Flag

Days from last treatment administration = Date of Death (see definition above) – Treatment Last date
If patient died = 'Y' and date of death is missing then Days from last treatment administration = Unknown

A flag (*) is to be derived if difference is <= 28.

Most Probable Cause of Death

If death date is obtained from the death form, select the most probable cause reported in the same form, along with the corresponding details;
else if death date is obtained from the survival follow-up forms, select the most probable cause reported in the same form, along with the corresponding details;
else if death date is obtained from the AE forms, set 'Adverse Event' as the most probable cause, without any details.

If most probable cause of death = missing then report it as 'Unknown' in the analysis tables.

Relationship to Study Drug of Death

If death date is obtained from the death form, select the relationship reported in the same form.
Else if death date is obtained from the AE forms, select the relationship of the adverse event reported in the same form.
If relationship of death to study drug = missing and most probable cause of death is not PD, then report it as 'Unknown' in the outputs.

If death date is obtained from the survival follow-up forms (where relationship to study drug is not reported) and most probable cause of death is not PD, then report it as 'Unknown' in the outputs.

Autopsy Performed: 'Yes' Value Derived

Autopsy Performed: derive value 'Y' if date of autopsy and/or autopsy results is reported.

Hospitalization

Duration (Days)

((Date of Discharge – Date of Admission) + 1) is calculated if Ongoing not equal to 'Yes' or if Date of Discharge is not missing.

Weeks from First Dose Date

[(Date of admission – First Dose Date) + 1] / 7

LABORATORY TESTS

Safety Population

In principle, the outputs concerning laboratory examinations will be based on all patients who took any drug ever (Treated Patients). In most of the summary displays (e.g. contingency table) the number of Treated Patients is going to be the reference population for safety analyses. However, when specified, the subset of treated patients with at least one non-missing lab. Assessment (for the test under analysis within the time window to be displayed, e.g. cycle 1, cycles > 1, whole treatment period) may be considered, instead of the whole set of treated patients.

Reference Document for CTC Grade Calculation

The document to be referred to is the NCI CTCAE v.3.0 *(*http://ctep.cancer.gov/reporting/ctc_v30.html grading system. Not all the laboratory assays have a corresponding grading according to CTC. Also for some of the assays, the CTC reference document reports absolute values as thresholds that define the boundaries of the grade category, whereas the boundaries of many other assays are defined as multiples of either Upper or Lower Limit of Normality (LLN,ULN).

Additionally, although variations outside the normality ranges are pathological in both directions (above and below the limits) for the majority of the assays, in most cases the CTC grade has been defined in one direction only. For those assays whose abnormality is determined by two-way modifications *(e.g. Calcium, Sodium)* both abnormalities are to be analysed independently and the worst CTC grade should be calculated both for variations above and below the limit of normality. A variation that is abnormal in one direction is to be considered normal in the opposite one.
See CTC classification for references of lab. Assays with bidirectional CTC grade defined.

Low / High (L/H) Flag

This flag is stored in the Oracle DB and it marks the values according to where they fall with respect to their range of normality; it is derived as follows:
- <flag> = 'L' if: [both < value > and <lower range limit > are not missing] and <value> LT <lower range limit>
- <flag> = 'H' if: [both < value > and <upper range limit > are not missing] and <value> GT <upper range limit>
otherwise the flag will be N (printed as missing in some of the outputs).

Variables to used for CTC grade calculation

CTC grade is not collected on the CRF or stored in the Oracle DB, rather it is calculated as part of the analysis of safety data; the calculation will move from the following variables stored in the OC DB:

LBFCTC = Flag identifying lab tests included in the reference document.
LBVCTC = Assay Value Converted into CTC Unit.
RGLCTC = Low Value Converted into CTC Unit.
RGHCTC = High Value Converted into CTC Unit.
LBUCTC = Standard CTC Unit.

CTC units are the units associated to the boundary values reported in the reference document.
For those laboratory tests whose CTC boundary values are expressed in absolute value and for which in the reference document two different values and units were available (e.g. conventional and standard international), conventional units were preferred, therefore the above variables contain the conventional value, ranges and unit.
For those laboratory tests whose CTC boundary values are expressed as multiples of ULN and LLN (mainly belonging to Blood Chemistry, see below) the above variables contain the collected value, ranges and unit.

Converted Value, Unit and Range Limits

To the purpose of data presentation and analysis, each laboratory test should be expressed in the same unit across patients within the same test. Therefore a set of derived variables (converted value, unit and range limits) containing the harmonized values units and ranges is to be created according to the following rules.
For those test that belong to the CTC classification system the choice of units has been based on those reported in the reference document in the definition of the thresholds.
For all the other tests the conventional units are to be used.
In details:
Hematology:

- For lab. Tests reported in the reference document use the CTC Value and Unit variables (LBVCTC and LBUCTC).
  Warning for the programmer: if the collected value of *Neutrophils* and *Lymphocytes* (and/ or other ones to be specified) was originally expressed as % of WBC, the value stored in the OC variable LBVCTC and LBUCTC have already been converted in absolute count /mm^3, but the lab. Assay codes ('NEUT' and 'LYM') have not been changed accordingly in 'NEUTX' and 'LYMX' respectively.

- For lab. Tests not reported in the reference document the converted value will be expressed in the same unit of WBC (i.e. absolute count /mm^3), in particular, if *Eosinophils*, *Basophils, Monocytes* are expressed as % over the total count of WBC, they will be converted in absolute values. In summary:
  WBC total count * Lab. Test / 100 if the collected value is expressed as percentage of the WBC value;
  Lab. Test * 1000 if the collected value is expressed as $10^3/mm^3$ or as $10^9/L$.
  For *Blasts*, *Nucleated RBCs, Plasma Cells, Atypical Cells* the set of derived variables containing the harmonized values, units and ranges will be a copy of the Conventional set.

Blood Chemistry:

- For lab. Tests reported in the reference document whose CTC grades class boundaries are expressed in absolute value (e.g. Albumin, Uric Acid, Calcium, Phosphorus Inorganic, Potassium, Sodium,…) use the CTC Value and Unit variables.
- For lab. Tests reported in the reference document whose CTC grades are expressed as multiple of ULN and LLN (e.g: Alkaline Phosphatase, AST, ALT, Bilirubin, Creatinine….) use the Conventional Value and Unit variables.
- For lab. Tests not reported in the reference document use the Conventional Value and Unit variables.

Coagulation:

- For lab. Tests reported in the reference document (e.g. INR and aPTT) whose CTC grades are expressed as multiple of ULN and LLN use the Conventional Value and Unit variables.
- For lab. Tests not reported in the reference document (e.g. PT and PT % of control) use the Conventional Value and Unit variables.

Allocation of Lab. Tests to the Relevant Study Period

Laboratory tests are key examinations for the evaluation of the safety of the patients on treatment with the experimental compound(s)/regimen.
Blood samples are repeatedly collected during study conduct according to study specific schedule of events as outlined in the protocol. Lab assessments scheduled at the end of each cycle (or at baseline when cycle 1 is considered) should be performed on the day before first day of cycle or at latest on the same day, but in any case before actual treatment administration. As per CRF compilation instructions, these assessments belong to the cycle that is about to complete and not to the cycle that is about to start.
In other words, if a lab assessment is performed on the same day of first drug administration of the cycle, it is considered to have been performed before that the drug administration took place.
Based on this assumption, whether or not the assessments were recorded at the right cycle in the CRF, in the individual data listing the values will be reported within the study period of pertinence and analysed consistently.
To this purpose the assessments performed on the same date as the first day of treatment administration in the cycle are to be allocated as follows should they be recorded in the wrong cycle in the CRF.

Cycle 1:

- If lab. Assessment $date_{Cycle\ 1}$ is not missing and if (assessment $date_{Cycle\ 1}$) ≤ (treatment $date_{Cycle\ 1}$) then lab. $Assessment_{Cycle\ 1}$ should be considered along with pretreatment laboratory assessment.
- Else if (assessment $date_{Cycle\ 1}$) > (treatment $date_{Cycle\ 1}$) then no allocation should be performed and the specific lab. $Assessment_{Cycle\ 1}$ should be considered along with all other cycle 1 lab. Assessments.

Any Cycle >1:

- If lab assessment date$_{Cycle\ x}$ is not missing and if (assessment date$_{Cycle\ X}$) ≤ (treatment date$_{Cycle\ X}$) then lab assessment$_{Cycle\ X}$ should be allocated to the previous cycle X-1 with a valid treatment administration record, and considered along with the lab assessments of Cycle (X-1) for the data analysis.
- Otherwise no allocation should occur and the specific lab. Assessment$_{Cycle\ X}$ should be considered along with all other cycle X lab. Assessments.

Allocation of lab. Tests to the relevant study period is the first step to be performed. Both original and allocated cycles values should be stored as two distinct variables in the analysis database.

Allocation of Lab. Tests Reported at Cycles with Missing Treatment Dose or Date

Lab. Tests recorded at a cycle for which the total administered dose is missing or the cycle start date is missing should be allocated to the previous available cycle with a valid treatment administration record and should be considered together with the tests of that cycle of treatment.

Allocation of Lab. Tests Reported at 28 days AE Visit

Lab. Tests performed at the 28 days AE visit are expected to be reported in the CRF as assessments of last cycle, therefore no action is taken.

Laboratory test day

Laboratory test day is calculated after the allocation process as :

(lab.assessment date – treatment start date) before first study drug administration (i.e. when lab.assessment date ≤ treatment start date)

(lab.assessment date – start date of cycle) + 1 on treatment (i.e. when lab.assessment date > treatment start date)

where: start date of cycle is the date of the first dose administration in the cycle to which the test was allocated

If lab. Assessment date is missing laboratory test day is not to be derived.

Cycles with at Least One Assessment

Treatment cycles with at least one assessment: for each laboratory test it is a cycle with a valid (non missing) value for the given test after the allocation process.

Treated Patients with at least one Assessment

Treated patients with at least one cycle with at least one assessment for the specific laboratory test

Baseline Data: Value, Unit, CTC Grade and Date

After the allocation process, for each analyzed test, select the most recent value among the pretreatment assessment(s).
The following information should be recorded in the analysis database: Baseline Value, Unit, CTC Grade and Date.

Worst CTC grade

For lab. Test included in the NCI CTCAE v.3.0 reference document, it is the first occurrence, after the allocation process, of the highest CTC grade observed during the time window of reference, i.e.: baseline, cycle 1, cycles >1, all cycles.

Lab. CTC Grade 3 – 4 Flag

In the listings all occurrences of CTC grades 3 or 4 must be flagged, e.g. by an asterisk: for instance "3 * " or "4 * "

OTHER SAFETY ASSESSMENTS

Temperature

In the Outputs use "Temperature in Celsius".

Blood Pressure

Blood Pressure Flags

At pretreatment

At pretreatment a '*' sign is to be derived to identify systolic blood pressure ≥ 140 mmHg OR diastolic blood pressure ≥ 90 mmHg

On Treatment

(1) Systolic Blood Pressure ≥ 140 mmHg
OR
(2) Diastolic Blood Pressure ≥ 90 mmHg
OR
(3) Systolic Blood Pressure – Baseline Systolic Blood Pressure ≥20 mmHg.
OR
(4) Diastolic Blood Pressure – Baseline Diastolic Blood Pressure ≥10 mmHg.
A '*' sign is to be derived for (1) and (2), a '§' sign is to be derived for (3) and (4).

Blood Pressure: Normal and Abnormal Values

'**Normal**': if systolic blood pressure < 140 *AND* diastolic blood pressure < 90.
'**Abnormal**': Else, if not normal (systolic blood pressure ≥ 140 *OR* diastolic blood pressure ≥ 90.
'**Unknown**': both values missing

Tabular display

At pretreatment:
Consider the most recent not "Unknown" of the assessments (if more than one) performed at pretreatment
Worst Assessment on treatment:
"Abnormal" if at least one assessment on treatment is "Abnormal". Else "Normal".

Electrocardiogram

Electrocardiogram: Category

If abnormality code begins with 'A' then category = Rhythm
If abnormality code begins with 'B' then category = P-wave morphology
If abnormality code begins with 'C' then category = Conduction
If abnormality code begins with 'D' then category = QRS
If abnormality code begins with 'E' then category = ST-T wave

In the summary tables, pts are counted for each reported category. If multiple abnormalities are reported in a category, the pt is counted once in the category.

Electrocardiogram: 'Yes' Value Derived

If any specific abnormality is marked on CRF, the patient is to be classified as 'YES' even though a missing or NO answer was reported to the initial question. In the outputs Derived 'Y' are to be identified by *

Electrocardiogram: Abnormalities not Present at Pretreatment

Abnormalities recorded after treatment start that were not already present at pretreatment are to be identified by *.

Electrocardiogram: Tracing Abnormalities (Y/N)

Tabular display
On treatment: Any abnormality = 'YES' / 'Abnormal' if at least one abnormality was recorded on the CRF or was derived (see above) after treatment start

Chest X-Ray

Days to/from Treatment Start

At pretreatment: (Date of Chest X-Ray – Study Treatment Start Date)
At any other assessment time: ((Date of Chest X-Ray – Study Treatment Start Date) + 1)

Pregnancy Test

Positive results are to be identified by '*'.

OTHER INFORMATION

Other Anti-tumor Therapies at Follow-up

'Yes' Value Derived

If any details are reported in CRF, the patient is to be classified as 'YES' even though a missing or NO answer was reported in the CRF

Days from Last Treatment Administration

Days from last treatment administration = Date of start of other anti-tumor therapies at FU– Treatment Last date.
If date of start of other anti-tumor therapies at FU is incomplete no calculation will be done.

Concomitant Medications

Any Concomitant Medications?: 'Yes' Value Derived

If any details are reported in CRF, the patient is to be classified as 'YES' even though a missing or NO answer was reported in the CRF

Duration (days)

((Concomitant Medication Stop Date – Concomitant Medication Start Date) +1) is calculated if stop date is not missing.

Weeks from Tr. Start Date

[(Concomitant Medication Start Date – Treatment Start Date) + 1] / 7

Concomitant Radiotherapies

Any Concomitant Radiotherapies?: 'Yes' Value Derived

If any details are reported in CRF, the patient is to be classified as 'YES' even though a missing or NO answer was reported in the CRF

Duration (days)

((Concomitant Radiotherapy End Date – Concomitant Radiotherapy Start Date) +1) is calculated if end date is not missing.

Weeks from Tr. Start Date

[(Concomitant Radiotherapy Start Date – Treatment Start Date) + 1] / 7

Blood Derivatives

Weeks from Tr. Start Date

[(Blood Derivatives Date – Treatment Start Date) + 1] / 7

REVISION HISTORY

Version	Date	Reviewed by: *(Printed name)*	Reason for change
1.0	**8th July 2013**		**First release of document**

Reviewed and Approved by:

Role	Printed Name	Signature	Date
Statistician	**Anna Petroccione**		
CL	**Marcella Martignoni**		