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Title page

A Randomized, Double-blind Phase III Study of Copanlisib versus Placebo in Patients with Rituximab-refractory Indolent Non-Hodgkin's Lymphoma (iNHL) – CHRONOS-2

Phase III copanlisib in rituximab-refractory iNHL

Bayer study drug	BAY 80-6946 / Copanlisib		
Study purpose:	Assess the efficacy and safety of copanlisib		
Clinical study phase:	III	**Date:**	02 FEB 2021
Study No.:	BAY 80-6946 / 17322	**Version:**	3.0
Author:	PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

AE	Adverse event
ATC	Anatomical-Therapeutic-Chemical
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
e.g.	For example, exempli gratia
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRFs	Electronic case report forms
EOT	End of treatment
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
GCP	Good Clinical practice
h	Hour(s)
i.e.	That is, id est
ICF	Informed consent form
IgM	Immunoglobulin M
iNHL	Indolent Non-Hodgkin's lymphoma
IV	Intravenous
LPL	Lymphoplasmacytoid lymphoma
M-1	Metabolite 1
M&S	Modeling & Simulation
MALT	Marginal-zone lymphoma of mucosa-associated lymphoid tissue
MedDRA	Medical Dictionary for Regulatory Activities

mg	Milligram
mmHg	Millimeter of mercury
MUGA	Multiple gated acquisition
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's lymphoma
NMZL	Nodal marginal-zone lymphoma
NYHA	New York Heart Association
OEE	Overall extent of exposure
PD	Progressive disease
PK	Pharmacokinetic
PT	Preferred Term
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis report
SAS	Statistical Analysis System
SFU	Safety follow-up
SLL	Small lymphocytic lymphoma
SMZL	Splenic marginal-zone lymphoma
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Table, figure, listing
WHO	World Health Organization

WHO-DD	WHO Drug Dictionary
WM	Waldenström macroglobulinemia

1. Introduction

Indolent NHLs encompass the following low-grade histologic subtypes of B-cell NHL included in the 2008 World Health Organization (WHO) classification of lymphoid neoplasm: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL), which is defined as Waldenström's macroglobulinemia (WM) when associated with a monoclonal immunoglobulin M (IgM) component and bone marrow involvement, splenic marginal-zone lymphoma (SMZL), nodal marginal-zone lymphoma (NMZL) and marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) (1). FL is the second most common subtype of NHL with 25% of newly diagnosed cases (2), followed by MALT lymphoma with 7% of all NHLs, while other subtypes are rather rare, with SLL, LPL, SMZL and NMZL accounting for 3%, 2%, 2% and 1% of NHL patients, respectively.

Indolent NHLs have a relatively good prognosis with a median survival longer than 10 years, but they are incurable with current available therapeutic options, especially in advanced stages. There are no guideline recommendations or widely accepted standards of care for patients beyond first relapse. The treatment given depends on the patient's condition, physician's preference, and availability of drugs not already used in previous lines of treatment. There is therefore a need for drugs with new targets and mechanisms of action that are effective and have a safety profile different from that of drugs used in earlier lines of treatment.

Copanlisib, a small molecule PI3K inhibitor, is a targeted agent that works by controlling the signaling pathway relevant for the survival and proliferation of iNHL cells. It is currently under investigation in various trials enrolling cancer patients and it has been approved for FL in the U.S. The evaluation of copanlisib's anticancer activity via a clinical trial design that controls for the natural history of tumor growth minimizes investigator bias in assessing treatment outcomes.

The original protocol, Version 1.0, is dated 20 MAY 2014. This statistical analysis plan (SAP) v3.0 describes the final analysis for study 17322 and is based on the integrated clinical study protocol Version 6.0 (protocol amendment 6), dated 01 DEC 2017. Following sponsor's decision to stop enrollment due to lack of feasibility to complete this study in reasonable time frame as protocol amendment 5 became effective, limited number of patients will be included in the analyses. The safety analyses will be performed as per the protocol. For other changes please refer to section 7 in this SAP.

2. Study Objective

The primary objective of this study is:

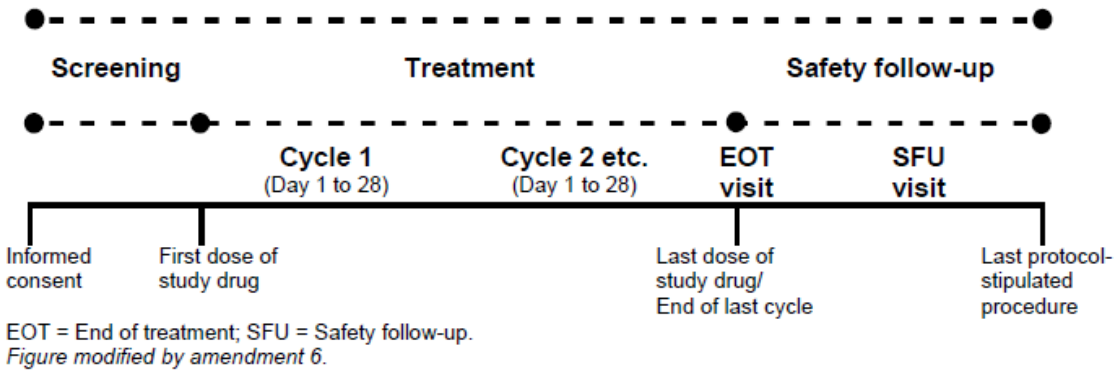
- To assess the safety of copanlisib.

3. Study Design

Initially this was a randomized, double-blind, two-arm Phase III study to evaluate the efficacy and safety of copanlisib as monotherapy in comparison to placebo in patients with rituximab-refractory iNHL. However, following sponsor's decision to stop enrollment on 03 MAR 2017 due to lack of feasibility to complete this study in reasonable time frame, the study design was modified as protocol amendment 6 became effective. All patients on study treatment will be offered to continue treatment with copanlisib after unblinding procedures are completed.

The overview of study periods is presented in Figure 3–1.

Figure 3–1 Study Periods

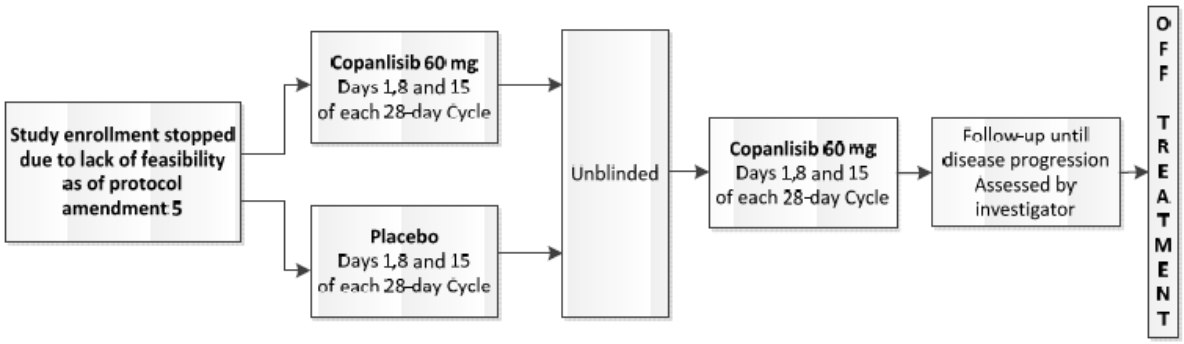


EOT = End of treatment; SFU = Safety follow-up.
Figure modified by amendment 6.

The start of the study period is defined by signing of the informed consent form (ICF).

A graphical presentation of the overall study design as of amendment 5 is shown in Figure 3–2.

Figure 3–2: Overall Study Design



Schedule of procedures is presented in the protocol amendment 6, Table 7–1.

Treatment Period

The start of the treatment period is defined by first administration of study drug (Copanlisib or placebo). Copanlisib will be administered IV over approximately 1h at starting dose of 60 mg on Days 1, 8 and 15 of each 28-day treatment cycle. Treatment will be continued until progressive disease (PD) by radiological assessments or clinical progression (tumor evaluations will be made at intervals that comply with the institution's standard of care [per investigator's assessment]), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. Before unblinding, patients in the placebo arm will receive a placebo IV infusion at the same schedule as that of Copanlisib arm. However, when placebo patients had PD before unblinding cut-off, they can choose to switch to Copanlisib and continue to stay in the study.

Disease progression (PD) defined in the Lugano Classification (3) and the Owen criteria (4) for patients with WM will be assessed.

All patients, after unblinding procedures are completed, will be offered an opportunity to continue this clinical study and receive active treatment with Copanlisib. Patients who are on Copanlisib treatment at the time of unblinding will continue Copanlisib treatment. Patients who are on placebo at the time of unblinding will switch to Copanlisib treatment after unblinding procedures are completed. After individual patient unblinding, patients receiving placebo, who switch to Copanlisib will have all study assessments reset to the initial schedule of study evaluations (i.e. as if the patient was restarted the study at Cycle 1 Day 1).

An End-of-treatment (EOT) visit will be performed within 7 days after the decision is made to discontinue study treatment.

Safety Follow-up Period

Following completion of the EOT visit, patients will enter the Safety follow-up. The Safety follow-up (SFU) visit will take place 30 days (window of +5 days allowed) after the last administration of study drug.

All patients who have already completed the safety follow-up visit at the time the amendment 6 becomes effective will discontinue the study.

4. General Statistical Considerations

4.1 General Principles

Statistical analyses will be conducted by or under the supervision of the sponsor's Study Statistician, except for the analysis of biomarker data, which, if considered to be performed, will be performed by or under the direction of the sponsor's Genomics and Biomarker Statistical Expert. Statistical analyses will be performed by using the software package Statistical Analysis System (SAS) release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

Due to the decision of stopping enrollment, limited number of patients will be included in the analyses. Therefore, the statistical analyses included in this study will be focused on descriptive statistics on safety variables only. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

Definition of safety endpoints, analyses strategies, structure of analyses datasets and layout of analyses data displays are following Bayer standards as documented in the Bayer standard system: Clinical Copanlisib Project Standards, Oncology Therapeutic Area Standards, and Global Medical Standards, respectively. Where the given ordering reflects the priority of the different standards that is specifications of the latter ones have to be followed only if not specified in standards mentioned before. Study-specific specifications may be included in addition to the project standards, if needed.

4.2 Handling of Dropouts

A patient who discontinues study participation prematurely (i.e., prior to disease progression) for any reason is defined as a "dropout" if the patient has already entered treatment.

Patients who drop out will not be replaced.

The number of patients who prematurely discontinue the study and study treatment for any reason, as well as the reasons for premature discontinuation of study treatment, will be reported.

4.3 Handling of Missing Data

In order to achieve the goal of a well conducted clinical trial according to Good Clinical Practice (GCP), every effort should be made to collect all data. However, despite best efforts, it may be inevitable that missing or incomplete data are reported. All missing or partial data will be presented in the patient data listing as they are recorded on the Case Report Form (CRF). Unless noted, missing data will not be estimated or carried forward in any statistical analysis.

The general principle for imputing dates is as follows:

If an adverse event start date is completely missing or partially missing, then it assumed that the start date occurs at the earliest time on-treatment whenever possible.

If a concomitant medication date is completely missing or partially missing, then the stop date is imputed to maximize the duration of the concomitant treatment. It should be noted that imputation of stop dates only applies to concomitant medications that are not ongoing.

4.4 Interim Analyses and Data Monitoring

No interim efficacy analyses are planned for this study.

A Data Monitoring Committee (DMC) is instituted to maximize the safety of the patients participating in the study. The DMC includes at least three members, including an independent Statistician and Oncologist. Safety review meetings were held as per separate DMC charter.

The report, including tables, listings, and figures, were generated by an independent statistician from a Statistical Analysis Center (SAC). The format and content of these data summaries were specified separately from this study SAP.

Decisions on trial termination, amendment, or cessation of patient recruitment based on risk/benefit assessment were made after recommendations from the DMC have been assessed by the sponsor.

No DMC meeting is planned after the DMC meeting on 21 JUN 2017 with the recommendations that the study can continue with finishing follow-up and there is no need for another safety meeting as this was considered as a close-out meeting.

4.5 Data Rules

If time intervals are to be displayed other than days in statistical evaluations, then one year is considered to have 365.25 days (average length of a year, including leap years), one month is considered to have 30.44 days (average length of a month, including leap years), one week is considered to have 7 days, and one cycle is considered to have 28 days (i.e. 4 weeks).

Baseline

Baseline is defined as the last available measurement performed prior to the first dose of Copanlisib/placebo study drug administration at Cycle 1 Day 1 for the patients who initially received Copanlisib/placebo. For the patients who initially received placebo and switched to Copanlisib after unblinding, baseline is defined as the last available measurement prior to the first dose of Copanlisib after switching.

Repeated measures

If there are repeated measurements per time point (e.g. laboratory values, vital signs, etc.), the following rules will be used (unless otherwise specified):

- Before the start of the study drug administration (i.e., for screening and baseline value), the latest measurement at scheduled visits will be used. Unscheduled visits will be used, if there are no measurements at pre-baseline or baseline scheduled visits. If the latter is the case, the last unscheduled visit will be used.
- In case of repeated measurements at any post-baseline time point, the first value of the scheduled measurements at that time point will be used. No unscheduled measurements will be used for any time points besides screening / baseline even when measurements at scheduled visits are missing.

5. Analysis Sets

5.1 Assignment of analysis sets

Full analysis set (FAS)

All patients who were randomized to treatment arms at the start of the study will be included in the FAS. Protocol deviation, demographics, baseline characteristics, medical history, prior and concomitant medication, prior and concomitant anti-cancer therapy will be summarized in the FAS.

Safety analysis set (SAF)

All patients with at least one administration of study drug will be included in the SAF. The SAF will be used for the analyses of study drug exposure, safety and efficacy variables.

All patients with valid pharmacokinetic (PK) data may be analyzed in the evaluation of PK concentrations and parameters.

Patients who signed the informed consent but were not assigned to treatment will be considered screening failures. They will be listed separately.

6. Statistical Methodology

Disposition, protocol deviations, demographics, baseline cancer characteristics, medical history, prior and concomitant medication, prior and concomitant anti-cancer therapy, drug exposure, efficacy and safety variables will be summarized separately for 2 groups including patients

- who were randomized to copanlisib until the end of study (copanlisb group)
- who were randomized to placebo until switching from placebo to copanlisib after PD or after unblinding (placebo group)

Disposition, protocol deviations, concomitant medication, concomitant anti-cancer therapy, drug exposure, efficacy and safety variables will also be summarized separately for patients who switched from placebo to copanlisib.

6.1 Population characteristics

6.1.1 Disposition

Disposition will be described by randomized treatment group (Copanlisib / placebo) for overview and the study phases of screening, treatment, safety follow-up, active follow-up and survival follow-up. Primary reasons for discontinuation from each study phase will be summarized.

Disposition for overview and screening will be summarized for all enrolled patients. Disposition for treatment will be summarized for full analysis set. Disposition for safety follow-up will be summarized for safety analysis set.

6.1.2 Protocol Deviations

The summary table for patients with major and minor protocol deviations will be summarized for full analysis set. Listings for major protocol deviations and COVID-19 related protocol deviations will be provided.

6.1.3 Demographic and Baseline Characteristics at Study Entry

Demographics and baseline characteristics are documented on the electronic Case Report Forms (eCRFs) of Demography and vital signs at baseline.

The following demographics and additional baseline characteristics at study entry will be summarized for full analysis set:

- Age (Years) and Age group (years) <65 and >=65
- Sex
- Medical history of diabetic (Diabetic / Non-diabetic)
- Medical history of arterial hypertension (With / Without)
- Ethnicity (Not Hispanic or Latino / Hispanic or Latino / Not reported)
- Race (White / Black / Asian / American Indian or Alaska Native / Native Hawaiian or Other Pacific Islander / Not reported)
- BMI=weight (kg) / [height (m)]^2

6.1.4 Cancer and Other Characteristics at Study Entry

Cancer and other baseline characteristics are reported on the eCRFs of Classification of Non-Hodgkin's Lymphoma, ECOG Performance Status, Systemic Anti-Cancer Therapy (Prior), Vital Signs at baseline, and Cardiac Disease (NYHA assessment).

The following cancer and other baseline characteristics will be summarized for full analysis set:

- Histology of tumor at study entry
- Follicular lymphoma (FL) grade at study entry, if FL
- Follicular Lymphoma International Prognostic Index (FLIPI) (5) score (for patients with FL) at study entry
- Staging of tumor (Ann Arbor classification) at study entry
- Number of prior systemic cancer therapy lines (1-3, 3-5, >5)

- Infiltration seen in bone marrow biopsy as per local assessment
- Time from initial diagnosis to randomization (months)
- Time from most recent progression to randomization(months)
- Time since first progression to randomization (months)
- Number of baseline target lesions (Total number and frequency by group 1-3, 4-6)
- Number of baseline non-target lesions (Total number and frequency by group 1-3, 4-6, 7-8, >8)
- Serum IgM level (for WM only) (mg/dL) at baseline
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- New York Heart Association (NYHA) classification (Class I / Class II / Class III / Class IV / Not applicable) at baseline
- Systolic Blood Pressure (mmHg) at screening
- Diastolic Blood Pressure (mmHg) at screening
- Baseline HbA1c

6.1.5 Medical History

Medical history (i.e., relevant previous diagnoses, diseases or surgeries) not pertaining to the study indication, that started before signing of the informed consent and considered relevant to the study will be presented by MedDRA version 22.1 or higher Primary System Organ Class (SOC) and Preferred Term (PT). All medications and significant non-drug therapies taken within 30 days (window of +5 days allowed) before study entry will be recorded and summarized for full analysis set.

6.1.6 Prior and Concomitant Medication

Prior and concomitant medications will be coded by the *World Health Organization Drug Dictionary* (WHO-DD) Version MAR 2020 or higher.

Prior and concomitant medications will be summarized based on WHO-DD Anatomical-Therapeutic-Chemical (ATC) drug class and drug name for full analysis set.

Any medication that has been stopped after first administration of study treatment (Copanlisib/ placebo) is considered as concomitant and otherwise as prior. Note that the same medication can appear more than once in the table as it can have several ATC codes.

6.1.7 Prior and Concomitant Anti-cancer Therapy and Procedures

The prior anti-cancer therapy and procedures are recorded on the eCRFs Diagnostic and Therapeutic Procedures (Prior) for iNHL, Systemic Anti-Cancer Therapy (Prior) and Radiotherapy (Prior). The concomitant anti-cancer therapy and procedures are recorded on the eCRFs Diagnostic and Therapeutic Procedures (Concurrent) for iNHL, Systemic Anti-Cancer Therapy (during Follow-Up) and Radiotherapy (during Follow-Up).

The minimum, median, and maximum number of prior systemic anti-cancer therapy lines as well as number of patients with 1, 2, 3, ≥4 lines of therapy will be summarized by treatment group for FAS. Time since last systemic anti-cancer therapy will be summarized using descriptive statistics by treatment group for FAS. The time between the start day of last course of systemic anti-cancer therapy and the day of confirmation of the most recent

progression will also be displayed as a classification table, showing proportions of patients with ≤ 6 months vs. > 6 to <12 months vs. ≥ 12 months, by treatment group.

The following anti-cancer therapy will be summarized by treatment group for FAS:

- prior and concurrent diagnostic and therapeutic procedure
- prior and follow-up radiotherapy
- prior and follow-up systemic therapy

6.1.8 Study Drug Administration

Descriptive statistical summaries of study drug exposure will be provided for the following variables:

- Overall extent of exposure (OEE) in days:

Defined as the time from the first administration of the first study treatment (day_{first}) until the last administration of the last study treatment (day_{last}), including 7 additional days in order to consider the weekly dosing regimen, is calculated as:

OEE (days) = $day_{last} - day_{first} + 7$.

- Number of cycles
- Number of infusions during treatment phase and categorized by 1-6, 7-12, 13-18 and etc.
- Total dose actually administered (mg)

OEE will include interruptions/delays during treatment. As a general rule, and in accordance with the Therapeutic Area Standard oncology team and the timing concept, trailing "0 mg" records (not followed by any positive amount of drug), will not be included in the calculation of any drug duration or amount. Similarly, the according trailing "drug interruptions" will not be used in statistical tables. A footnote will be included, stating that "Interruption becoming permanent study treatment discontinuation before resumption of study treatment is not accounted as an interruption".

For patients with dose modification, the total number (%) of subjects with dose reductions, interruptions/delays, re-escalations and the total number (%) of dose reductions, interruptions/delays, re-escalations and the reasons will be summarized. Number of reduction, interruption/delay and re-escalation per subject will also be summarized.

6.2 Efficacy

Due to the limited number of patients enrolled in this study, the study efficacy objectives and analyses were removed and the tumor assessment was stopped to be collected since 01 DEC 2017. Summary of tumor response by investigators' assessment will be provided. Progression-free survival and best overall response will also be listed.

Best overall response (BOR)

BOR is defined as the best response per Cheson criteria (ordered CR, PR, SD, PD, NE) and per Owen criteria (ordered CR, very good partial response (VGPR), PR, Minor response(MR),

SD, PD, NE) over all post-treatment assessments on or prior to the first progression. Tumor assessments after first PD and after start of new anticancer therapy are not considered for best overall response.

Objective response rate (ORR)

ORR is assessed in all patients up to the time of analysis of PFS. ORR is defined as the proportion of patients who have a best response rating over the whole duration of the study (i.e. until time of analysis of PFS) of complete response (CR) or partial response (PR) according to Cheson criteria Lugano Classification and for patients with WM a response rating of CR, very good partial response (VGPR), PR, or minor response (MR) according to Owen Criteria.

Progression-free survival (PFS)

For patients who were randomized to copanlisib until the end of the study and who were randomized to placebo until switching to copanlisib after PD or after unblinding, PFS is defined as the time (in months) from the randomization date to first disease progression or death due to any cause, if death occurs before progression is documented.

For patients who switched from placebo to copanlisib, PFS is defined as the time (in months) from the start date of copanlisib to first disease or death due to any cause, if death occurs before progression is documented.

For details for radiological tumor assessments see protocol section 7.3.2 and for details for tumor assessments in patients with WM see protocol section 7.3.3.

PFS for patients without PD or death at the time of analysis will be censored at the last actual date of tumor assessment or last biochemical assessment for patients with WM without lesions evaluable by imaging.

6.3 Safety

Safety variables will include treatment-emergent adverse events (TEAEs), laboratory parameters, ECG, cardiac function, vital signs and other safety measures.

6.3.1 Adverse Events

Adverse Events (AEs) will be coded using *Medical Dictionary for Regulatory Activities* (MedDRA) dictionary Version 22.1. Severity of AEs will be graded using the NCI-CTCAE v4.03. AEs will be classified by the investigator as related or not related to study drug.

Treatment emergent adverse events (TEAEs)

TEAEs are defined as any event arising or worsening after start of study drug administration until 30 days (window of +5 days allowed) after the last study drug administration (end of Safety follow-up). More specifically, for the patients who received Copanlisib until the end of study and the patients who received placebo until switching to Copanlisib after PD or after

unblinding, the start of study drug administration is referring to the start of Copanlisib or placebo after randomization. For the patients switching from placebo to Copanlisib, the start of study drug administration is referring to the start of Copanlisib drug administration after switching. See Section 4.3 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

An overall summary of the following TEAEs by MedDRA (SOC) and (PT) will be provided for safety analysis set:

- Any TEAEs
- Any treatment emergent serious adverse events (TESAEs)
- Any TEAEs leading to discontinuation
- Any TEAEs leading to dose modification
- Any TEAEs related to protocol procedure
- Any study drug related TEAEs
- Any study drug related treatment TESAEs
- Any study drug related TEAEs leading to discontinuation
- Any study drug related TEAEs leading to dose modification

The following will be summarized by MedDRA system organ class (SOC) and preferred term (PT), and by worst grade based on Common Terminology Criteria Adverse Event (CTCAE) v. 4.03.

- TEAEs
- TEAEs with incidence ≥10%
- Grade 3-5 TEAEs
- Treatment related TEAEs
- Treatment related TEAEs incidence ≥5%
- Grade 3-5 treatment related TEAEs
- TESAEs
- Grade 3-5 TESAEs
- Treatment related TESAEs
- Any TEAEs leading to discontinuation
- Any TEAEs leading to dose interruption
- Any TEAEs leading to dose reduction
- Any drug related TEAEs leading to discontinuation
- Any drug related TEAEs leading to dose interruption
- Any drug related TEAEs leading to dose reduction

The maximum severity of the TEAEs will be summarized according to the NCI-CTCAE toxicity criteria. For each patient, multiple occurrences of the same event will be counted once at their maximum severity within a SOC and PT.

Adverse Events of Special Interest

Non-infectious Pneumonitis is defined as AE of special safety interest. The Standardized MedDRA Query (SMQ) 'Interstitial lung disease' with narrow search (i.e. category 2A) will be used to select these AEs of special interest. The only relevant NCI CTCAE code is AETOXCOD=RTPNM (pneumonitis).

Summary of patients with Non- infectious pneumonitis/Interstitial lung disease requiring corticosteroids, antibiotics, or both will be displayed descriptively. All patients with TEAEs of special interest by worst CTCAE grade, study drug relatedness and seriousness will be listed.

COVID-19 relevant adverse events

The COVID-19 relevant adverse events will be identified using a high-level term (HLT) of coronavirus infection via latest MedDRA version. A subject listing of these AEs will be provided. The serious AEs will be flagged in the listing.

AE listings

Subject listings will be provided for serious TEAEs, TEAEs leading to discontinuation, TEAEs leading to interruptions and reductions and TEAEs of special interests including the worst CTCAE grade, study drug relatedness, and seriousness.

Death

Summary table and listings will be provided for

- Subjects who died during treatment or up to 30 days (window of +5 days allowed) after last dose of study medication
- Subjects who died later than 30 days (window of +5 days allowed) after last dose of study medication

6.3.2 Pregnancies

The results of pregnancy tests will be listed by specimen type, patient ID, visit and result (positive/negative). Any pregnancy will be documented.

6.3.3 Clinical Laboratory Evaluations

Results of the clinical laboratory evaluations (coagulation, hematology, chemistry and urinalysis) by worst CTCAE grade post-baseline will be summarized. Changes in worst grade of laboratory toxicities at last pre-treatment value compared to worst grade post-baseline value is also provided. Worst grades for laboratory toxicities will be calculated according to CTCAE, version 4.03 based on laboratory measurements.

Summary statistics on the values and changes from baseline will also be presented for each quantitative clinical laboratory variable, at each post-baseline visit. For tables displaying

treatment-emergent laboratory abnormalities, patients with specimen collection between start of treatment and 30 days (window of +5 days allowed) after EOT will be included.

6.3.4 Hyperglycemia

Hyperglycemia adverse events using specific MedDRA PT grouping 'MLG Hyperglycemia' will be summarized by treatment group and by NCI CTCAE worst grade for TEAEs and TESAEs.

In addition to the above summary, specific HbA1c evaluation will be performed for each analysis group including at baseline and post-baseline-mean, classified by diabetic/non-diabetic.

Patients will be categorized according to their baseline HbA1c values as

- $< 5.7\%$
- $\geq 5.7\% - < 6.5\%$
- $\geq 6.5\%$.

Within each group, the descriptive statistics for HbA1c values at end of treatment visit will be summarized by treatment group and medical history of diabetic/non-diabetic. Shift table for classified HbA1c values from baseline to end of treatment by treatment group and medical history of diabetic/non-diabetic will also be provided.

Glucose in CTCAE grade will be displayed by treatment group and medical history of diabetic/non-diabetic at pre-dose and at post-dose 0 h, 1 h and 2 h after the end of study drug infusion on Cycle 1 Day 1 and at pre-dose and at post-dose 1 h after the end of study drug infusion on subsequent visit.

For patients with hyperglycemia adverse events, the number of patients using antihyperglycemic treatment with drug start date on or after their first treatment-emergent adverse event will be summarized in overall, and separately for the WHO-DD ATC classes for a) insulin and analogues and b) Blood glucose lowering drugs, excluding insulins. In addition, these summaries will be presented separately for the subgroups of patients with vs without history of diabetes.

6.3.5 Vital Signs

Results of vital signs will be summarized by visit, including change from baseline where appropriate.

6.3.6 Hypertension

The blood pressure measurements will be recorded on the vital sign eCRF:

- Systolic blood pressure (mmHg, measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion on infusion days)

- Diastolic blood pressure (mmHg, measured at 0 h (pre-dose), 30 min (mid-infusion), 60 min (end of infusion); and 1 h and 2 h after the end of infusion on infusion days)

The number of patients with abnormal post-dose systolic/diastolic blood pressure will be displayed by visit and worst post-dose TEAE hypertension grade by treatment group and medical history of arterial hypertension/no medical history of arterial hypertension. For this purpose post-dose systolic/diastolic blood pressure values will be categorized according to CTCAE, version 4.03: Grade 1 (systolic 120-139 mmHg or diastolic 80-89 mmHg); Grade 2 (systolic 140-159 mmHg or diastolic 90-99 mmHg); Grade 3 (systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg), grade 4 Life-threatening consequences; urgent intervention indicated.

Hypertension adverse events will be presented using MLG grouping of MLG Hypertension for TEAEs and TESAE,

For patients with hypertension adverse events, the number of patients using antihypertensive treatment with drug start date on or after their first treatment-emergent adverse event will be summarized descriptively. In addition, the number of patients requiring antihypertensive treatment will be presented separately for the subgroups of patients with vs without history of hypertension.

6.3.7 Electrocardiogram (ECG) and Cardiac Function

The overall interpretation of the ECG (normal/abnormal, clinical relevance) and the ECG findings will be recorded on the 12-Lead Safety ECG page of CRF. The overall interpretation of the MUGA scan/echocardiogram and findings will be recorded on the Cardiac function (MUGA/echocardiogram) page of CRF. Frequency table for overall interpretation of the 12-lead ECG and the ECG diagnosis, as well as the overall interpretation of the echocardiogram and the corresponding diagnosis will be summarized by visit. Listing of clinically significant abnormal cardiac findings will be provided

6.4 Pharmacokinetics/pharmacodynamics

By the time the protocol amendment 6 became effective, no further PK samples were collected. However, blood samples already collected may be used for the PK analysis. Individual concentration-time data of Copanlisib and M-1 may be provided in a clinical study report appendix. Further population PK analysis is described in a separate Modeling & Simulation (M&S) Plan and results will be reported separately in the M&S Report (Branch Trial 20068).

6.5 Biomarker evaluation

The analysis of the exploratory biomarker data, which, if considered to be performed, will be performed by or under the direction of the sponsor's Genomics and Biomarker Statistical Expert. This will be described and reported separately.

7. Document history and changes in the planned statistical analysis

- Approval of SAP v1.0 on 13 APR 2016

- SAP v2.0 updated on 14 MAR 2018 according to the protocol amendment 6 on 01 DEC 2017

- Changes in the planned statistical analysis in SAP v3.0

Due to the suspension of enrollment in Chronos-2 study, only a limited number of subjects has been enrolled. As discussed with Regulatory, instead of performing two sets of analyses: unblinding analysis (cut-off 1) and final analysis (cut-off 2) described in the Protocol, the analysis has been simplified. Disposition, protocol deviations, demographics, baseline cancer characteristics, medical history, prior and concomitant medication, prior and concomitant anti-cancer therapy, drug exposure and safety variables will be summarized separately for 2 groups including patients

- who were randomized to copanlisib until the end of study (copanlisb group)
- who were randomized to placebo until switching from placebo to copanlisib after PD or after unblinding(placebo group)

Disposition, protocol deviations, concomitant medication, concomitant anti-cancer therapy, drug exposure, efficacy and safety variables will also be summarized separately for patients who switched from placebo to copanlisib.

In this statistical analysis plan, progression-free survival will be performed in lieu of the protocol mentioned efficacy evaluation of time to progression.

8. References

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