NOVARTIS

Clinical Development

MCS110

CMCS110Z2102 / NCT02807844

A Phase Ib/II, open label, multicenter study of MCS110 in combination with PDR001 in patients with advanced malignancies

Statistical Analysis Plan (SAP)

Author: [redacted], Trial Statistician

Document type: SAP Documentation

Document status: Final version 2.0

Release date: 29-JUN-2020

Number of pages: 39

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
24-May-2016	Prior to FPFV	Creation of final version	N/A – First version	NA
29-JUN-2020	Prior to DBL	Final for approval	Amendment 1	Section 1.1 Study design Section 1.2 Study objectives and endpoints Section 2.1 Data analysis general information Section 2.1.1 General definitions Section 2.2 Analysis sets / Withdrawal of ICF / Subgroups Section 2.4.1 Study treatment/compliance Section 2.5.1 Primary endpoints Section 2.5.2 Statistical hypothesis, model, and method of analysis Section 2.5.4 Supportive analyses Section 2.7.1 Secondary endpoints Section 2.8 Safety analyses Section 2.8.3 Laboratory data [redacted] Section 3 Sample size calculation Section 5.5 Rule of exclusion criteria of analysis sets

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AR	Accumulation Ratio
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BLRM	Bayesian Logistic Regression Model
CBR	Clinical Benefit Rate
CK	Creatine Kinase
CL	Clearance
Cmax	maximum drug concentration
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CSP	Clinical Study Protocol
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dose Administration Record
DCR	Disease Control Rate
DDS	Dose-determining Set
DI	Dosing Intensity
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRL	Drug Reference Listing
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
irRC	Immune-related Response Criteria
IB	Investigator’s Brochure
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic
PDI	Planned Dose Intensity
PDS	Programming Datasets Specifications

PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial Response
Q2W, Q3W, Q4W	Respectively, every two, three, four weeks
RAP	Report and Analysis Process
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase two Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TFL	Tables, Figures, Listings
TNBC	Triple Negative Breast Cancer
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CMCS110Z2102 that will be presented in the Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Table Figure Listing (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document.

All changes to the planned analysis described in this document required before or after database lock will be made through an amendment or addendum, respectively. Note that obvious corrections will be made at the time of analysis to address minor formatting or spelling mistakes present in the TFL shells document without the need to amend.

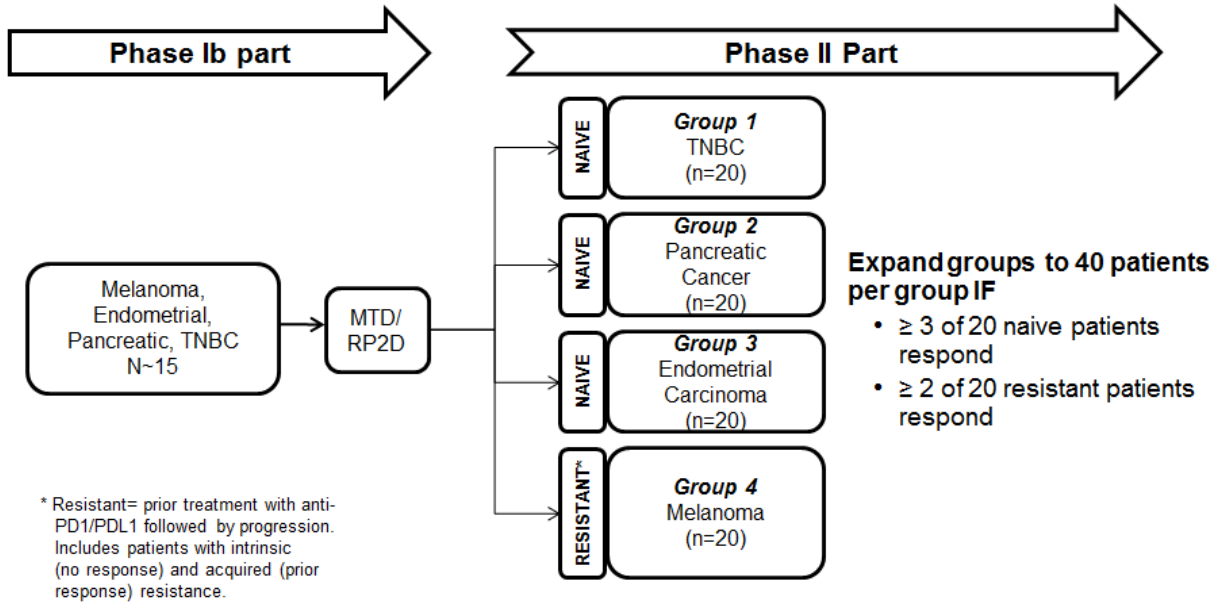
The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., MTD/RP2D declaration, IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

RAP documents, including SAP and TFL shells, were created based on final protocol version 05 released on 23 July, 2019.

1.1 Study design

This study is a phase Ib/II, multi-center, open-label study starting with a phase Ib dose escalation part followed by a phase II part. MCS110 and PDR001 will be administered i.v. every three weeks (Q3W) until the patient experiences unacceptable toxicity, progressive disease as per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients should not discontinue treatment based on progressive disease per RECIST v1.1. The study design is summarized in Figure 1-1.

Figure 1-1 Study design



Phase Ib part

During the phase Ib part of the study, cohorts of patients will be treated with increasing doses of MCS110 and PDR001 every three weeks until a RP2D is determined for this treatment combination.

It is expected that an RP2D will be established before the MTD is reached. The RP2D for the combination will not exceed the RP2Ds for the single agent administration of MCS110 and PDR001. To assure that the combination RP2D does not exceed the MTD, combination MCS110 and PDR001 dose escalation will also be guided by an adaptive Bayesian logistic regression model (BLRM) following the escalation with overdose control (EWOC) principle. At least 15 patients are required during dose escalation to define the MTD; however, fewer than 15 patients may be treated if the RP2D is determined without reaching the MTD (for further details see [CMCS110Z2102-CSP-Section 6.2.3]).

Phase II part

Once the MTD and/or RP2D have been declared, additional patients will be enrolled in the Phase II part in order to assess the preliminary anti-tumor activity of MCS110 in combination with PDR001.

In the phase II part, patients will be assigned to different groups depending on the tumor type as shown in Figure 1-1. Please refer to [CMCS110Z2102-CSP-Section 5.1] for further details.

All groups will enroll approximately 20 patients each. Enrollment to any of these groups may be stopped at fewer patients if achieving these enrollment targets is not logistically feasible. For groups 1 and 3, the sample size may be extended to approximately 40 patients, if at least 3 patients out of the first 20 treated in that group have an objective response (CR or PR) per RECIST v1.1 or irRC. Twenty patients will be enrolled into Group 2 at RP2D. Enrollment may be expanded up to approximately 40 patients if clinical benefit per RECIST v1.1 or irRC (CR, PR or SD > 4 months) is observed in at least 3 pts. In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criteria is met. Group 4 may similarly be expanded if at least 2 patients out of the first 20 treated in that group have an objective response. A Bayesian design will be used in order to estimate ORR within each expansion group. Details of the sample size calculations leading to the patient numbers are provided in [CMCS110Z2102-CSP-Section 10.8].

The primary CSR will be based on all patients' data from the phase Ib and phase II parts, up to the time when all patients have completed at least six cycles of treatment or discontinued treatment. Patients who are on study beyond cycle 6 may remain on treatment until they discontinue the study. Any additional data (after the data cut-off date for the primary CSR) will be further summarized in a final CSR at completion of the study, as defined in [CMCS110Z2102-CSP-Section 4.3].

1.2 Study objectives and endpoints

Objectives and related endpoints are described in Table 1-1 below.

Table 1-1 Objectives and related endpoint

Objective	Endpoint	Analysis
Primary		
Phase Ib part:		
To characterize the safety and tolerability of MCS110 given in combination with PDR001 and to identify a recommended dose combination for Phase II.	Frequency, severity and seriousness of AEs, laboratory abnormalities and other safety parameters. Dose interruptions, reductions, and dose intensity.	Refer to Section 2.8
	Incidence rate of dose limiting toxicities (DLTs) during the first two cycles of study treatment.	Refer to Section 2.5.2.1
Phase II part: To estimate the anti-tumor activity of the combination of MCS110 with PDR001	-Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (groups 1, 3 and 4). -Clinical benefit rate (CBR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1), which is defined as confirmed objective response or SD > 4 months. (Group 2)	Refer to Section 2.5.2.2
Secondary		
Phase Ib part:		
To estimate the preliminary anti-tumor activity of the combination of MCS110 with PDR001	ORR, progression free survival (PFS), clinical benefit rate (CBR), duration of response (DOR) and disease control rate (DCR) per RECIST v1.1 and per immune related Response Criteria (irRC)	Refer to Section 2.7
Phase II part: To further characterize the safety and tolerability of MCS110given in combination with PDR001	Frequency, severity and seriousness of AEs, laboratory abnormalities and other safety parameters.	Refer to Section 2.8
Phase II part: To evaluate the preliminary anti-tumor activity of the combination of MCS110 with PDR001 by additional efficacy measures	ORR per irRC, PFS, DOR, DCR, CBR per RECIST v1.1 and per irRC (Group 1, 3 and 4) CBR per irRC, PFS, DOR, DCR, ORR per RECIST v1.1 and per irRC (Group 2)	Refer to Section 2.7
Phase Ib and Phase II parts:		
To characterize the pharmacokinetics of MCS110 and PDR001 in combination	Serum concentration of MCS110 and PDR001 and PK parameters	Refer to Section 2.9
To assess immunogenicity of MCS110 and PDR001	Presence and/or concentration of anti-PDR001 or anti-MCS110 antibodies	Refer to Section 2.9

Objective	Endpoint	Analysis
To describe survival with MCS110 and PDR001 in combination	Overall survival (OS)	Refer to Section 2.7

[redacted]

2 Statistical methods

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version 9.4, for Bayesian logistic regression model (BLRM) modeling, R version 3.0.2 and JAGS version 3.12 will be applied and for other bayesian analyses, R version 3.4.3 will be used. PK parameters will be calculated using non-compartmental methods available in Pharsight

Phoenix version 6.4 (or newer compatible version). Newer compatible version may be used for all programs. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant PK and PD measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data).

The study data will be analyzed and reported based on all patients' data of the Phase Ib and Phase II parts up to the time when all patients have potentially completed at least six cycles of treatment or discontinued the study. Phase Ib data and Phase II data will be reported separately. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported at completion of the study as defined in [CMCS110Z2102-CSP-Section 4.3].

The following rules will be followed for reporting results unless stated otherwise:

- Phase Ib dose escalation data: cohorts treated during the dose escalation with the same dose levels of MCS110 and PDR001 will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group and "All Phase Ib Subjects".
- Phase II data: All summaries, listings, figures for non-safety analysis will be reported by arm. Safety analysis of phase II will be reported by arm and "All Phase II Subjects" Column. The arms to which they were assigned at baseline based on disease types consist of the following:
  - Group 1: TNBC (naive to PD-1/PD-L1 directed therapy)
  - Group 2: Pancreatic cancer (naive to PD-1/PD-L1 directed therapy)
  - Group 3: Endometrial cancer (naive to PD-1/PD-L1 directed therapy)
  - Group 4: Melanoma (resistant to PD-1/PD-L1 directed therapy)

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Screen failure patients are those who signed the informed consent, but never started the study treatment for any reason. For these patients, the eCRF data collected (see [CMCS110Z2102-CSP-Section 7.1.1.1]) will not be included in analyses, but will be reported in the CSR as separate listings.

2.1.1 General definitions

Study drug and Study treatment

Study drug refers to the individual compound i.e., MCS110, or PDR001. The study treatment is defined as MCS110 in combination with PDR001, or single agent MCS110 or PDR001 if one of the study drugs needs to be discontinued.

Date of first/last administration of study drug and study treatment

The date of first (last) administration of study drug is derived as the first (last) date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF.

The date of first (last) administration of study treatment is derived as the first (last) date when a non-zero dose of any component of study treatment was administered and recorded on the Dosage Administration Record (DAR) eCRF. Dates of first/last administration of study treatment are defined as:

- Date of first administration of study treatment = min (first date of MCS110 administration, first date of PDR001 administration)
- Date of last administration of study treatment = max (last date of MCS110 administration, last date of PDR001 administration)

Study day

The study day for all assessments/events will be calculated using the start date of study treatment as reference. For assessments/events occurring on or after the start date of study treatment, study day will be calculated as:

Study day (days) = Event date – Start date of study treatment + 1

Therefore, the first day of study treatment is study day 1.

For all assessment/events occurring prior to the start of the study treatment, study day will be negative and will be calculated as:

Study day (days) = Event date – Start date of study treatment

Study day will be displayed in the data listings.

Baseline

Baseline is the last available and valid assessment performed or value measured within 21 days (28 days for baseline radiological evaluations) before the first administration of study treatment, unless otherwise stated under the related assessment section. Baseline can be the day before first treatment administration or the same day as first treatment administration if a pre-dose assessment/value is available (e.g., ECG, PK samples, [redacted]).

If time is recorded for the first treatment dose and for a specific assessment performed the day of first dose, this assessment will be considered as baseline only if it is actually performed before the first dose, as checked using both times.

If time is not recorded, a specific assessment performed the day of first dose administration will be considered as baseline if, according to protocol, it should be performed before the first dose.

[redacted]

[redacted]

Patients with no data on a particular parameter before the first treatment administration will have a missing baseline for this parameter.

For pregnancy test, baseline will be within 72 hours before first administration of study treatment.

Computation of baseline for ECG, [redacted] and other endpoints are described in each specific section.

On-treatment assessment/event

An on-treatment assessment/event is defined as any assessment/event obtained in the time interval from the start date of study treatment until the last date of study treatment (i.e., including combination partner) + 30 days inclusive.

Any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent efficacy assessments would be excluded from all relevant efficacy summary.

2.2 Analysis sets/Withdrawal of ICF/Subgroups

2.2.1 Full Analysis Set

The full analysis set (FAS) comprises all patients who received at least one dose of MCS110 or PDR001. Patients will be analyzed according to the planned treatment combination. Unless otherwise specified, FAS is the default set used for all analyses.

2.2.2 Safety Set

The safety set (SS) includes all patients who have received at least one dose of MCS110 or PDR001. Patients will be classified according to treatment received, where treatment received is defined as:

1. The treatment assigned if it was received at least once, or
2. The first treatment received when starting therapy with study treatment if the assigned treatment was never received.

The safety set will be used for the safety summary of the study.

2.2.3 Dose-determining Set

The dose-determining set (DDS) consists of all patients from the safety set in the phase Ib dose escalation part who either meet the following minimum exposure criterion and have sufficient safety evaluations, or have experienced a DLT during the first two cycles.

A patient is considered to have met the minimum exposure criterion if he/she received two doses of MCS110 and PDR001 during the first two cycles.

Patients who do not experience a DLT during the first two cycles are considered to have sufficient safety evaluations if they have been observed for ≥ 42 days following the first dose, and are considered by both the Sponsor and Investigators to have enough safety data to conclude that a DLT did not occur.

Patients who do not meet these minimum safety evaluation requirements nor experience a DLT will be regarded as ineligible for the DDS and an additional patient may be recruited (see [CMCS110Z2102-CSP-Section 7.1.3.1]).

2.2.4 Pharmacokinetic Analysis Set

The pharmacokinetic analysis set (PAS) includes all patients who provide an evaluable PK profile. A profile is considered evaluable if all of the following conditions are satisfied:

- Patient receives one of the planned treatments
- Patient provides at least one primary PK parameter

Patients will be classified according to planned treatment group.

The PAS will be used for summaries of PK concentration data, PK parameters [redacted]

2.2.5 Withdrawal of Informed Consent

Any data collected in the clinical database before informed consent is obtained and after a withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a patient withdraws full consent is recorded in the eCRF.

2.2.6 Subgroup of interest

Not applicable.

2.3 Patient disposition, demographics and other baseline characteristics

Unless noted otherwise, summaries and listings described in this section will be based on the FAS.

2.3.1 Patient disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still on-treatment (based on non-completion of the 'End of Treatment' page),
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment' page with discontinuation date entered),
- Primary reasons for study treatment discontinuation (based on discontinuation reason entered in the 'End of Treatment' page),

- Number (%) of patients who discontinued from post-treatment follow-up (based on completion of the 'End of Post Treatment Phase Disposition' page with discontinuation date entered),
- Primary reasons for post-treatment follow-up discontinuation (based on discontinuation reason entered in the 'End of Post Treatment Phase Disposition' page).

Protocol Deviation

Major protocol deviations leading to exclusion from analysis sets will be tabulated separately by treatment group for phase Ib and by patient group for phase II part. All protocol deviations will be listed. The full list of protocol deviations are documented in the Study Specification Document (SSD). Protocol deviations leading to exclusion from analysis sets and associated severity codes are specified in Section 5.3.

2.3.2 Demographics

Demographic data including age, sex, predominant race, ethnicity, baseline weight and WHO/ECOG performance status will be listed and summarized.

In addition, child bearing potential, pregnancy test results will be listed, and age (18-< 65, 65-< 85, ≥ 85 years) categories summarized.

2.3.3 Other baseline characteristics

Medical history

Medical history and current (ongoing) medical conditions, including cancer-related conditions and symptoms, will be listed. Medical history and current medical conditions are coded using the latest Medical Dictionary for Regulatory Activities (MedDRA v23.0) terminology available at the time of reporting.

Prior anti-neoplastic therapies

Prior anti-neoplastic therapies will be listed for medication, radiotherapy and surgery.

The number (%) of patients who received any prior anti-neoplastic medication, radiotherapy or surgery will be summarized, separately.

The summary of prior anti-neoplastic medications will include the total number of regimens (note: there can be more than one medication per regimen), setting at last medication, and time (in days) from start of last medication to progression.

The last medication is defined based on the last end date of all prior regimen components. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include the radiotherapy locations, (including all locations recorded for each patient) and setting at last radiotherapy.

The summary of prior anti-neoplastic surgery will include the time (in months) between the last surgery (non-biopsy procedure) to start of study treatment, procedure at last surgery (non-biopsy procedure) and residual disease at last surgery.

Consider specific imputation rules for patial dates in Section 5.1.4.

Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, histological grade, stage at initial diagnosis, time (in months) from initial diagnosis of primary site to start of study treatment, time (in months) since most recent recurrence/relapse or progression to start of study treatment, time (in months) from initial diagnosis of primary site to first recurrence/relapse or progression, current stage of cancer, current extent of disease (metastatic sites).

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The Safety Set will be used for all medication data summaries and listings.

2.4.1 Study treatment/compliance

Study treatment

MCS110 in combination with PDR001 (Q3W):

- Last date of ***exposure*** to study drug (MCS110) = last date of administration of MCS110 + 20 days
- Last date of ***exposure*** to study drug (PDR001) = last date of administration of PDR001 + 20 days
- Last date of ***exposure*** to study treatment (MCS110 + PDR001) = max (last date of MCS110 administration, last date of PDR001 administration) + 20 days = Date of last administrion of study treatment + 20 days

Planned treatment: Planned treatment is the treatment to which a patient is assigned during enrollment.

Received treatment: Please refer to Section 2.2.2.

Planned dose: Planned dose is the dose level(s) of study drug(s) corresponding to the planned treatment.

Prescribed dose: Prescribed dose is the dose level(s) of study drug(s) prescribed by doctor before study treatment is administered at beginning of each cycle.

Dose administered (mg/kg) for MCS110 = Dose prescribed (mg/kg) * Total volume administered (mL)/Total volume planned to be administered (mL);

Dose administered (mg) for PDR001 = Dose prescribed (mg) * Total volume administered (mL)/Total volume planned to be administered (mL);

Definitions of duration of exposure, cumulative dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), as well as intermediate calculations, are as follows:

- **Duration of exposure (days) to study drug:** last date of ***exposure*** to study drug − first date of study drug + 1 (periods of interruption are not excluded);

- **Duration of exposure (days) to study treatment:** last date of ***exposure*** to study treatment − first date of study treatment + 1 (periods of interruption are not excluded);
- **Duration of exposure (weeks)** = Duration of exposure (days)/7;
- **Cumulative dose:** sum of all dose administered (mg/kg) to a patient for MCS110; sum of all dose administered (mg) to a patients for PDR001;
- **Cumulative planned dose:** sum of all planned dose (mg/kg) of MCS110 that were intended to have been taken during the treatment period by a patient; sum of all planned dose (mg) of PDR001 that were intended to have been taken during the treatment period by a patient;
- **Number of doses scheduled per protocol :** number of doses given to a patient if each actual cycle length is exactly 21 days and study treatment is given on day 1 of each cycle, which is calculated as: [Duration of exposure to study drug (days)/ 21 (days)] + 1*I{ Duration of exposure to study drug (days) **mod** 21 (days) ≠ 0}. [x] is the largest integer less than or equal to x. b = mod(a, m) returns the remainder after division of a by m , where a is the dividend and m is the divisor. I{·} is a indicator function. This will be calculated for MCS110 and PDR001 separately and used for calculation of dose intensity below.
- **DI:**
  - For MCS110 (mg/kg/3wks): cumulative dose (mg/kg)/ number of doses scheduled per protocol during treatment period;
  - For PDR001 (mg/3wks): cumulative dose (mg)/ number of doses scheduled per protocol during treatment period;
- **PDI:**
  - For MCS110 (mg/kg/3wks): cumulative planned dose (mg/kg)/ number of doses scheduled per protocol during treatment period (i.e., this is equivalent to planned dose level);
  - For PDR001 (mg/3wks): planned cumulative dose (mg)/ number of doses scheduled per protocol during treatment period (i.e., this is equivalent to planned dose level);
- **RDI (%):**
  - For MCS110: 100 × DI (mg/kg/3wks)/PDI (mg/kg/3wks)
  - For PDR001: 100 × DI (mg/3wks)/PDI (mg/3wks)

Note: If a patient is still on treatment at the time of data cut-off, the end date of study treatment/drug will be replaced by the data cut-off date and the above respective algorithm will be used.

Dose interruption: Actual dose equal to zero, between the first and last non-zero doses, following a non-zero actual dose.

Dose reduction: A non-zero actual dose that is less than the immediate previous non-zero actual dose (if not the first dose) and below the treatment received dose.

Note: actual dose for MCS110 (mg/kg) = Dose prescribed (mg/kg) * Total volume administered (ml)/Total volume planned to be administered (ml); actual dose for PDR001 (mg) = Dose prescribed (mg) * Total volume administered(ml)/Total volume planned to be administered(ml).

The duration of exposure to each of the two study drugs and study treatment (including categories: ≤ 3, 3-≤ 6, 6-≤ 9, 9-≤ 12, 12-≤ 15, 15-≤ 18, > 18 weeks) will be summarized. In addition, the cumulative dose, DI, and RDI (including categories: < 0.5, 0.5-< 0.75, 0.75-< 0.9, 0.9-< 1.1, ≥ 1.1) will be summarized for each study drug.

To assess tolerability, the number (%) of patients who have dose reductions and interruptions , and the corresponding reasons, will be provided for each study drug. The number of dose reductions and interruptions per patient will be summarized for each study drug.

All doses of the study treatment along with reasons for any dose change will be listed.

Compliance

Compliance to study drug will be evaluated by dose reduction and dose interruption.

2.4.2 Concomitant therapies

Concomitant therapies are defined as any medications (excluding study treatment and antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and are recorded in the Concomitant Medications/significant non-drug therapies eCRF. These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system.

Any concomitant therapies starting prior to or after the start of study treatment will be listed.

Concomitant and significant non-drug therapies will be summarized by ATC class and preferred term to include medications or therapies starting on or after the start of study treatment but starting no later than 30 days after last dose of study treatment.

All medications or therapies starting prior to the first dose of study treatment and continuing after the start of study treatment will be listed.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.1.2). No imputation will be performed for concomitant medication end dates.

2.4.3 Anti-neoplastic therapies since discontinuation

Any anti-neoplastic therapies since discontinuation of study treatment will be listed.

2.5 Analysis of the primary objective

Phase Ib

The primary objective of the Phase Ib part is to characterize the safety and tolerability of MCS110 given in combination with PDR001 and to identify a recommended dose for Phase II.

Phase II

The primary objective of the Phase II part of this study is to estimate the anti-tumor activity of the combination of MCS110 with PDR001 in each expansion group.

2.5.1 Primary endpoint

2.5.1.1 Phase Ib part

The primary variables of Phase Ib are:

- Safety: Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs, and ECGs;
- Tolerability: Dose interruptions, reductions, and dose intensity;
- Incidence of DLTs in the first two cycles of study treatment.

2.5.1.2 Phase II part

For TNBC, endometrial carcinoma and melanoma the primary variable of Phase II is the Overall Response Rate (ORR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) based on local Investigator assessment, as defined in RECIST v1.1. Estimation of the true ORR in this part of the study will be based upon the observed BOR for patients in the FAS, using a Bayesian analysis.

For pancreatic patients, the primary variable of Phase II is the Clinical Benefit Rate (CBR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) (with at least two assessments 4 weeks apart) or stable disease (SD) > 4 months based on local Investigator assessment, as defined in RECIST v1.1. Estimation of the true CBR in this part of the study will be based upon the observed BOR for patients in the FAS, using a Bayesian analysis.

2.5.2 Statistical hypothesis, model, and method of analysis

2.5.2.1 Phase Ib part

2.5.2.1.1 Identification of a recommended dose

The dose escalation part of this study will be guided by a Bayesian analysis of first two cycles dose limiting toxicity (DLT) data for MCS110 and PDR001 in combination based on dose-determing set (DDS). If the two doses in first 2 cycles differs for one patient, the lower dose will be considered as the dose level from conservative aspect. The Bayesian analysis will be based on a model with three parts, representing:

- Single agent MCS110: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$; $d_1^* = 5$ mg/kg Q3W
- Single agent PDR001: $\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$; $d_2^* = 300$ mg Q3W
- Interaction: $\text{Odds}(\pi_{12}(d_1,d_2))) = \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$

$= \exp(\eta(d_1/d_1^*)(d_2/d_2^*))(\pi_1(d_1) + \pi_2(d_2) - \pi_1(d_1)\,\pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2)))$,

where $\text{logit}(\pi.(d.)) = \log[\pi.(d.)/\{1- \pi.(d.)\}]$, $d_1^* = 5$ mg/kg and $d_2^* = 300$ mg are the reference doses of MCS110 and PDR001 respectively, $\alpha_1, \alpha_2, \beta_1, \beta_2 > 0$ and $-\infty < \eta < \infty$.

Single agent toxicity is modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these

odds with an additional model parameter (odds multiplier). Details of the model are given in [CMCS110Z2102-CSP-Section 14.4].

Assessment of patient risk

After each cohort of patients, the posterior distribution for the risk of DLT for new patients at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0 , 0.16)
Targeted toxicity:	[0.16 , 0.33)
Excessive toxicity:	[0.33 , 1]

The escalation with overdose control (EWOC) principle

Dosing decisions are guided by the escalation with overdose control principle (Rogatko 2007). A combination dose may only be used for newly enrolled patients if the risk of excessive toxicity at that combination dose is less than 25%.

Prior distributions

For each single agent model, a mixture prior was derived. For MCS110, this study uses a mixture prior consisting of two components. Component 1 is the distribution derived based on dose-DLT data. The assigned weight for component 1 is 80%. Component 2 allows for a higher toxicity case. The assigned weight for component 2 is 20%. For PDR001, this study uses a mixture prior consisting of three components. Component 1and 2 are derived based on dose-DLT data. The assigned total weight for component 1 and 2 is 80%. Component 3 allows for a higher toxicity case. The assigned weight for component 3 is 20%.

A meta-analytic-predictive (MAP) approach was used to derive component 1 of the prior distribution for the single agent MCS110 model parameters, and component 1 and 2 of the prior distribution for the single agent PDR001 model parameters. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data (see Spiegelhalter 2004, Neuenschwander 2010, Neuenschwander 2014). MAP priors are derived from hierarchical models, which take into account possible differences between the studies.

For this study, available clinical data were taken from the following clinical studies:

For MCS110: [CMCS110A2101] first-in-human MCS110 study. This study is completed. [CMCS110X2201] a Phase II study in PVNS patients. This study is ongoing.

For PDR001: [CPDR001X2101] first-in-human PDR001 oncology study. This study is ongoing.

For each of the single agent prior, an additional high toxic component is introduced to allow for a higher toxicity case. A full description of the application of the MAP approach to derive the prior distributions of the single agent MCS110 and PDR001 model parameters is given in [CMCS110Z2102-CSP-Section 14.4].

The prior distribution for the interaction parameter was based upon prior understanding of possible drug safety interactions (see [CMCS110Z2102-CSP-Section 1.3.3]). This prior allows for the possibility of either synergistic or antagonistic interaction, and is fully described in [CMCS110Z2102-CSP-Section 14.4].

Listing of DLTs

DLTs will be listed, and their incidence summarized by primary system organ class and preferred term and worst grade (CTCAE version 4.03). Listings and summaries will be based on the DDS.

2.5.2.1.2 Safety and tolerability analyses

See Section 2.8 for details of analysis.

2.5.2.2 Phase II part

A Bayesian design will be used in order to estimate ORR (Group 1, 3 and 4) or CBR (Group 2) for each of the following groups in the Phase II part of the study.

- Group 1: MCS110 + PDR001, TNBC (naïve to PD-1/PD-L1 directed therapy)
- Group 2: MCS110 + PDR001, Pancreatic adenocarcinoma (naïve to PD-1/PD-L1 directed therapy)
- Group 3: MCS110 + PDR001, Endometrial carcinoma (naïve to PD-1/PD-L1 directed therapy)
- Group 4: MCS110 + PDR001, Melanoma (progressed on previous PD-1/PD-L1 therapy)

Each group will enroll approximately 20 patients, and may be extended to 40 patients (if at least 3 patients have an objective response for group 1, 2 and 3;and if at least 2 patients have an objective response for group 4). In addition, an exploratory group of 20 patients ar as lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if at least 3 patients have an objective response for group 2. See timing of the decision-making in [CMCS110Z2102-CSP-Section 4.2]. The primary analysis will be performed when all patients have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

Group 1, 3: Minimally informative unimodal Beta prior distribution are defined such that the prior mean ORR is set to be equal to 30% and the parameters of the minimally informative Beta prior distribution of ORR have been set up as following:

- $a/(a + b) = 0.3$
- $a = 0.43$
- $b = 1$.

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. Once updated, the estimate ORR and probability of ORR lies in the following categories will be reported:

- [0%, 15%] unacceptable efficacy
- [15%, 30%] moderate efficacy
- [30%, 100%] clinically relevant efficacy

If the observed ORR is equal to or greater than 30% (i.e. ≥ 12 responses (CR or PR) of out 40 patients) then this will be considered as preliminary evidence of antitumor activity of MCS110 + PDR001 in the respective patient group naive to PD-1/PD-L1 directed therapy.

Group 2: Minimally informative unimodal Beta prior distribution is defined such that the prior mean CBR is conservatively set to be equal to 15% and the parameters of the minimally informative Beta prior distribution of CBR have been set up as following:

- $a/(a + b) = 0.15$
- $a = 0.18$
- $b = 1$.

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. If the lower MCS110 dose level is explored (Group 2b), a separate model with the same prior assumption will be used to estimate CBR.

Once updated, the estimate CBR and probability of CBR lies in the following categories will be reported:

- [0%, 7.5%] unacceptable efficacy
- [7.5%, 15%] moderate efficacy
- [15%, 100%] clinically relevant efficacy.

Observed CBR will be analyzed by dose level. If the observed CBR is equal to or greater than 15% (i.e. ≥ 6 responses (CR, or PR, or SD for at least 4 months) out of 40 patients at RP2D; or ≥ 3 responses (CR, or PR, or SD for at least 4 months) out of 20 patients at lower dose group (Group 2b) then this will be considered as preliminary evidence of antitumor activity of MCS110 + PDR001 in the pancreatic patient group naive to PD-1/PD-L1 directed therapy.

Note that, for a sample size of n = 40, if the observed CBR is 15% then the posterior probability of true CBR greater than 7.5% is 93.5%; for a sample size of n = 20, if the observed CBR is 15% then the posterior probability of true CBR greater than 7.5% is 84.3%.

Group 4

Minimally informative unimodal Beta prior distribution are defined such that the prior mean ORR is conservatively set to be equal to 15% and the parameters of the minimally informative Beta prior distribution of ORR have been set up as following:

- $a/(a + b) = 0.15$
- $a = 0.18$
- $b = 1$.

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. Once updated, the estimate ORR and probability of ORR lies in the following categories will be reported:

- [0%, 7.5%] unacceptable efficacy
- [7.5%, 15%] moderate efficacy
- [15%, 100%] clinically relevant efficacy.

If the observed ORR is equal to or greater than 15% (i.e. ≥ 6 responses (CR or PR) of out 40 patients) then this will be considered as preliminary evidence of antitumor activity of MCS110 + PDR001 in the respective patient group resistant to PD-1/PD-L1 directed therapy.

2.5.3 Handling of missing values/censoring/discontinuations

Patients in the dose escalation part who are ineligible for the DDS will be excluded from the primary analysis, although their data will be used for all remaining analyses.

Patients in the phase II part who have BOR of unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the primary analysis of ORR according to RECIST v1.1.

If any alternative cancer therapy is taken while on study any subsequent efficacy assessments would be excluded from all relevant efficacy summary.

Continuing events (e.g., AEs, concomitant medication, etc.) will be summarized using the data cut-off date as the date of completion, with a flag to indicate within listings that the event is continuing. For patients who discontinue the study with ongoing events, the discontinuation date will be used as the completion date of the event.

The reason for discontinuation from study will be summarized and listed.

Other missing data will simply be noted as missing on appropriate tables/listings.

2.5.4 Supportive analyses

Not applicable.

2.6 Analysis of the key secondary objective

Not applicable.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

2.7.1.1 Phase Ib part

Overall response rate (ORR), Progressive Free Survival (PFS), Clinical Benefit Rate (CBR), Duration of Response (DOR), Disease Control Rate (DCR) per RECIST v1.1 and per immune related Response Criteria (irRC), and Overall Survival (OS).

2.7.1.2 Phase II part

For Group 1, 3 and 4: ORR per irRC, PFS, DOR, DCR, CBR per RECIST v1.1 and per irRC, and OS.

For Group 2: CBR per irRC, PFS, DOR, DCR, ORR per RECIST v1.1 and per irRC, and OS.

2.7.2 Statistical hypothesis, model, and method of analysis

Tumor response will be determined per local investigators' assessment, according to RECIST v1.1 and irRC. For the purpose of this study, Clinical benefit rate (CBR) is defined as the

proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD which lasts for a minimum time duration of 16 weeks (4 months).

For all efficacy parameters, data will be listed, summarized, or analyzed by treatment group for the phase Ib part, and by disease group (groups 1 to 4) for phase II patients treated at the MTD/RP2D.

Bayesian analysis described in Section 2.5.2.2 will be performed and reported based on response data per irRC.

ORR, CBR and DCR will be summarized with accompanying 90% confidence intervals.

PFS, along with DOR for patients who experience a CR or PR at any time on study will be listed by patient. PFS will be analyzed using Kaplan-Meier estimates (including graphical representation) with 90% CIs of median survival for each treatment group/disease group.

OS data will be listed for all patients enrolled in the Phase Ib and Phase II parts. Descriptive statistics for OS endpoint (e.g., median OS and 90% CI of the Kaplan-Meier estimates) will be provided if applicable by treatment group and furthermore by disease group for patients treated at the MTD/RP2D in the Phase II part.

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. Best overall response per RECIST v1.1 and per irRC will be listed and tabulated.

2.7.3 Handling of missing values/censoring/discontinuations

Patients in the phase II part who have BOR of unknown (UNK) or not assessed (NA) will be considered as a treatment failure in the secondary analysis of ORR according to irRC.

For the analysis of PFS, patients without documented disease progression or death are censored at the time of last valid tumor assessment documenting non-progression (one of complete response, partial response, or stable disease). Patients without any valid post-baseline tumor assessment response (one of CR, PR, SD, or PD) will be censored on the start date of treatment. Patients who have a PFS event (progression or death) after two or more consecutive missing assessments from the last valid tumor assessment will be censored on the last valid tumor assessment (or on the start date of treatment among those with only one valid postbaseline tumor assessment).

Other missing data will simply be noted as missing on appropriate tables/listing.

If any alternative cancer therapy is taken while on study any subsequent efficacy assessments would be excluded from all relevant efficacy summary.

2.8 Safety analyses

The assessment of safety is based on the type and frequency of Adverse Events (AEs) as well as on the number of laboratory values that fall outside of pre-determined ranges (Common Toxicity Criteria for Adverse Events (CTCAE) grading limits or normal ranges as appropriate). Other safety data include electrocardiogram and vital signs.

The safety set will be used for summaries and listings of safety data with the exception of DLTs for which the DDS will be used.

The overall observation period will be divided into three mutually exclusive segments:

1. pre-treatment period: from day of patient's informed consent to the day before first dose of study treatment
2. on-treatment period: from day of first dose of study medication to 30 days after the last dose of study treatment
3. post-treatment period: from 31 days after date of last administration of study treatment

Safety summaries will primarily be based on all data from the on-treatment period. Following last administration of study treatment, adverse events (including serious adverse events), and new antineoplastic therapies are collected for a period of 150 days for PDR001 and 90 days for MCS110. Following start of new antineoplastic therapy, only treatment related adverse events will be collected. Select summaries of related adverse events will be produced for the combined on-treatment and post-treatment periods for patients receiving PDR001 (see Section 2.8.1).

2.8.1 Adverse events (AEs)

Adverse events will be coded and graded using the latest version of MedDRA and CTCAE, respectively, available at the time of reporting. If CTCAE grading does not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study. Death information will be collected on the "Death" eCRF page.

Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

All AEs will be listed. All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, unless noted otherwise.

Summary tables for AEs have to include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The following AE summaries will be produced:

- AEs regardless of study drug relationship (including CTC grade 3-4)
- AEs suspected to be study drug related (including CTC grade 3-4)
- AEs regardless of study drug relationship leading to discontinuation of study drug
- AEs which are not SAEs regardless of study drug relationship (for CTRD)
- SAEs regardless of study drug relationship

A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event. A subject with multiple occurrences of an AE is counted only once in the AE category (e.g. system organ class, preferred term).

2.8.1.1 Adverse events of special interest / grouping of AEs

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to compound PDR001. These groupings are defined using MedDRA terms, SMQs (standardized MedDRA queries), HGLTs (high level group terms), HLT (high level terms) and PTs (preferred terms). Customized SMQs (Novartis MedDRA queries, NMQ) may also be used. A NMQ is a customized group of search terms which defines a medical concept for which there is no official SMQ available or the available SMQ does not completely fit the need. It may include a combination of single terms and/or an existing SMQ, narrow or broad.

For each specified AESI, number and percentage of subjects with at least one event of the AESI occurring during on-treatment period will be summarized.

Summaries of these AESIs will be provided by study treatment.

A listing of all grouping levels down to the MedDRA preferred terms used to define each AESI will be generated.

2.8.2 Deaths

All deaths occurred in the study will be listed with principal cause reported/preferred term and following summaries will be produced:

- All deaths with cause of death by primary system organ class and preferred term

2.8.3 Laboratory data

Laboratory data will be converted into SI units and classified (by Novartis Oncology Statistical Programming) into CTC grades according to CTCAE v4.03 as applicable. Grade 5 will not be used.

Baseline comparisons will be done based on shift tables but not considered for derivation of CTC grade.

Laboratory data for which a CTC grading does not exist will be classified into low, normal, or high based on local laboratory normal ranges as applicable.

The following summaries will be produced for hematology and coagulation, biochemistry, urinalysis parameters:

- For parameters with CTC grades: Shifts from baseline to the worst post-baseline CTC grade,
- For parameters with no CTC grades defined: Shifts from baseline to the worst post-baseline using low/normal/high classifications.

The following listings will be produced:

- Listing of all laboratory data with values flagged to show corresponding CTC grades and the classifications relative to the laboratory reference ranges (i.e., High (H) or Low (L)).

Both fasting glucose and non-fasting glucose will be summarized and listed for information integrity. Both of glucoses will be combined and reported based on CTCAE v4.03. Fasting glucose values will be flagged in the listing.

Table 2-1 and Table 2-2 lists all laboratory parameters that will be summarized.

Table 2-1 Laboratory parameters for which CTCAE grades are defined

Hematology and coagulation		Biochemistry		Urinalysis	
White Blood Cells (WBC)	↑↓	Creatinine	↑	Protein	↑
Hemoglobin	↓	Uric acid	↑		
Platelets	↓	Magnesium	↑↓		
Neutrophils(absolute or %)	↓	Calcium	↑↓		
Lymphocytes(absolute or %)	↑↓	Phosphate	↓		
Partial thromboplastin time (PTT)	↑	Albumin	↓		
Activated partial thromboplastin time (APTT)	↑	AST (SGOT)	↑		
International normalized ratio (INR)	↑	ALT (SGPT)	↑		
		Chloride	↓		
		Bicarbonate	↓		
		Total Bilirubin	↑		
		Glucose	↑↓		
		Alkaline Phosphatase	↑		
		Creatine kinase	↑		

↑ Indicates that CTC grade increases as the parameter increases.
↓ Indicates that CTC grade increases as the parameter decreases.

Table 2-2 Laboratory parameters (without CTCAE grades) for which lab reference ranges are defined

Hematology and coagulation	Biochemistry	Urinalysis
Prothrombin time (PT)	Blood Urea Nitrogen (BUN) or Urea	Specific gravity
Hematocrit	T3 [free]	Glucose
Basophils (absolute or %)	T4 [free]	Blood
Eosinophils(absolute or %)	TSH	Bilirubin
Monocytes(absolute or %)	Direct bilirubin	Ketones
	Indirect bilirubin	White Blood Cells
	Lactate dehydrogenase (LDH)	pH

A listing will be produced for the serum pregnancy test and only patients with positive test results will be included.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

Baseline for ECG analysis is defined as the average of all available ECG measurements associated with the baseline assessment. Scheduled study day 1 pre-dose ECGs will be

considered to have been obtained prior to study drug administration if dosing time is missing. If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

If a patient has more than one post-baseline measurement at a specific time point, the average of all available measurements associated with the nominal time point will be used for the analyses.

The following summary will be provided for each applicable ECG parameter:

- Frequency counts and percentages of patients having notable ECG values according to Table 2-3.

Table 2-3 Criteria for notable ECG values

ECG parameter	Criteria for ECG notable values
QTcF (ms) and QD (ms)	Increase > 30 ms to ≤ 60 ms Increase > 60 ms New > 450 to ≤ 480 ms New > 480 to ≤ 500 ms New > 500 ms
QRS (ms)	Increase > 25% and QRS > 120 ms New QRS > 120 ms
HR (bpm)	Increase > 25% and HR > 100 bpm Decrease > 25% and HR < 50 bpm
PR (ms)	Increase > 25% and PR > 200 ms New PR > 200 ms

Notable ECG values (including notable QT interval values) will be flagged in the listings.

2.8.4.2 Vital signs

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and weight (kg). Vital sign values considered notably abnormal are defined in Table 2-4.

Table 2-4 Criteria for notable vital sign values

Vital sign	Criteria for clinically notable vital sign values
Systolic blood pressure [mmHg]	≥ 180 mmHg/≤ 90 mmHg with increase/decrease from baseline of ≥ 20 mmHg
Diastolic blood pressure [mmHg]	≥ 105 mmHg/≤ 50 mmHg with increase/decrease from baseline of ≥ 15 mmHg
Pulse rate [bpm]	≥ 100 bpm/≤ 50 bpm with increase/decrease from baseline of ≥ 25%
Body temperature [°C]	≥ 39.1
Weight [kg]	≥ 10% decrease/increase from baseline

Patients with any clinically notable vital sign value will be listed.

2.8.4.3 Tolerability

Tolerability of study treatments will be assessed by summarizing the number of dose interruptions and dose reductions (see Section 2.4.1 for more details) by treatment group in the phase Ib part and by patient group in the phase II part. The reasons for dose interruption and dose reductions will be listed by patient and treatment group in the dose escalation part and by patient group in the dose expansion part; they will be summarized for each investigational drug by treatment group in the dose escalation part, and by patient group in dose expansion part. Cumulative dose, dose intensity and relative dose intensity will be summarized. Categories for relative dose intensity will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented.

2.9 Pharmacokinetics Analyses

The pharmacokinetic parameters will be determined by profiles using noncompartmental method(s) for both MCS110 and PDR001 as presented in Table 2-5, and PAS will be used in all pharmacokinetic data analysis and PK summary statistics. Patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analyses.

Table 2-5 Pharmacokinetic parameters to be analyzed

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass × time × volume-1)
AUCinf	The AUC from time zero to infinity (mass × time × volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The terminal half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the plasma (volume × time-1)
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)
Clast	Last observed quantifiable concentration (mass × volume-1)
AR	Accumulation Ratio=AUClast (multiple Dose)/AUClast (single dose) (for cycle 4 only)

For phase Ib part, descriptive statistics of all pharmacokinetic parameters in the Table 2-5 for both cycle 1 and cycle 4 will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum, by treatment group. For phase II part, descriptive statistics will be conducted for the pararmeters, including AUClast, AUCinf, Cmax, Clast, Tmax for both cycle 1 and cycle 4 and AR only for cycle 4 by patient group.

Summary statistics will be presented for MCS110 and PDR001 serum concentrations at each scheduled time point. Descriptive graphical plots of individual and mean serum/plasma concentration versus time profiles of free MCS110, PDR001 will be generated by treatment or patient group and cycle.

2.9.1 Data handling principles

Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

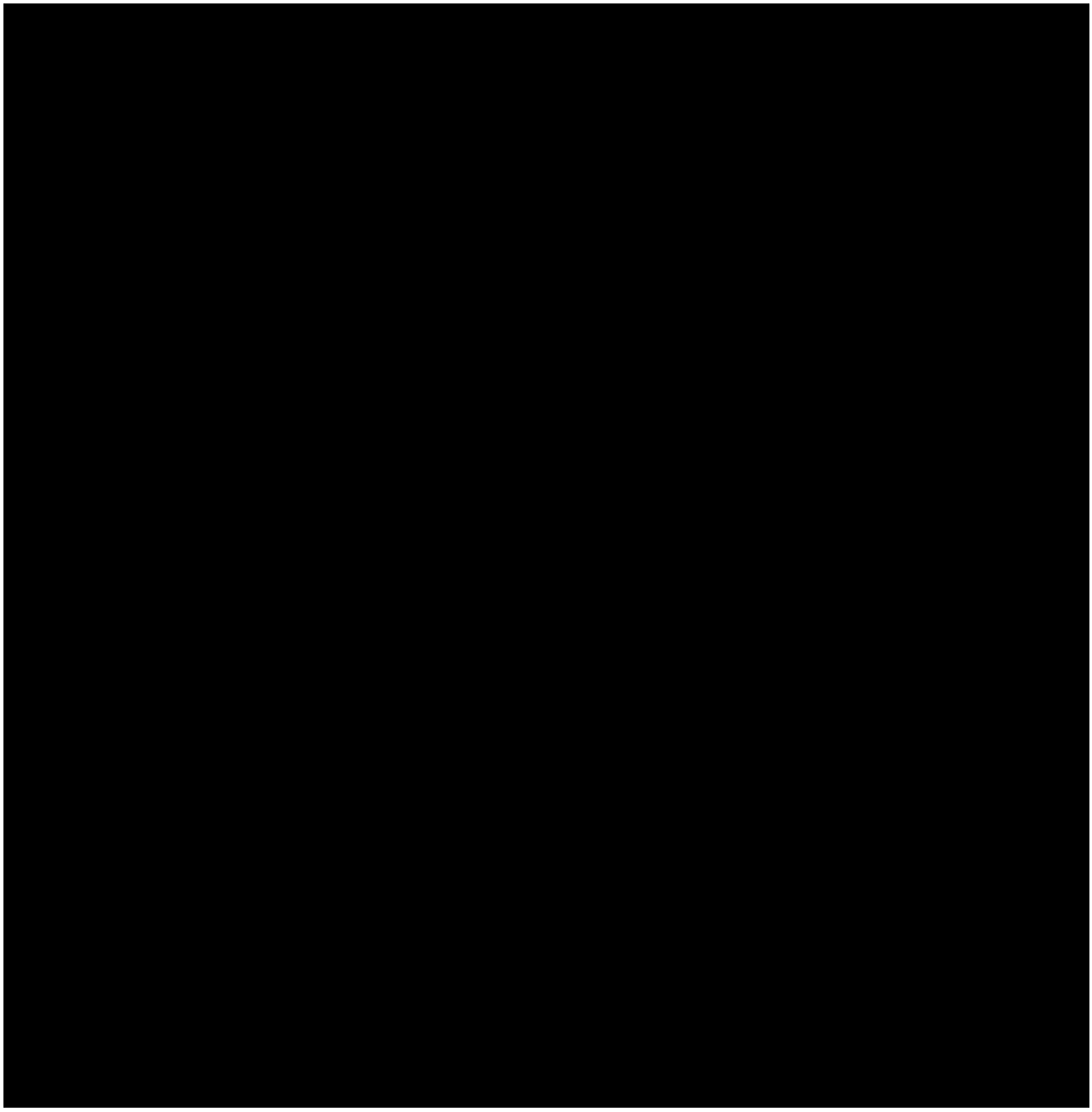
Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

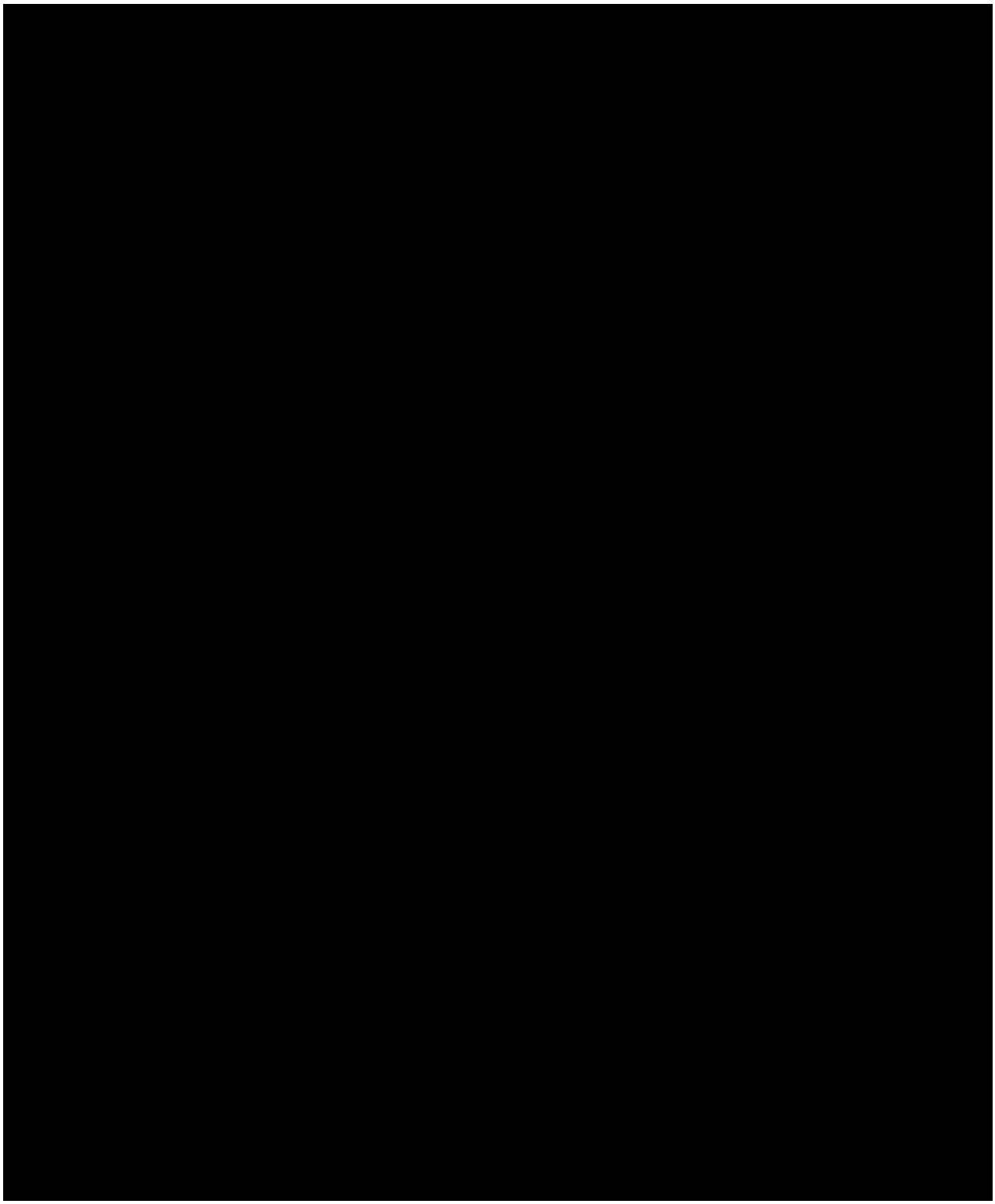
2.9.2 Immunogenicity

The presence and/or concentration of anti-MCS110 and/or anti-PDR001 antibodies, at each scheduled time point, will be listed by treatment group, disease and patient. Overall immunogenicity will be summarized when sample size is sufficient. Anti-MCS110 and/or anti-PDR001 antibody data will also be summarized. Number (%) of patients with positive immunogenicity will be calculated.

2.10 Patient-reported outcomes

Not applicable.





2.13 Interim analysis

Not applicable.

3 Sample size calculation

Phase Ib

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation phase including at least six patients at the MTD/RP2D level, as described in [CLSZ102X2101-CSP-Section 6.2.3]. Multiple cohorts may be sequentially enrolled to the same dose level. Additional cohorts of 3 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 15 patients are expected to be treated in the dose escalation phase for the model to have reasonable operating characteristics relating to its estimation of MTD.

Phase II

Approximately 20 patients will initially be enrolled to each of groups 1, 3 and 4. Enrollment may be expanded up to approximately 40 patients in these groups if objective responses (CR or PR) per RECIST v1.1 or irRC are observed (≥ 3 of 20 patients in each of the PD-1/PD-L1 therapy naïve groups or ≥ 2 of 20 patients in the PD-1/PD-L1 therapy resistant group)

([CMCS110Z2102-CSP-Section 2.2]). In Group 2, 20 patients will be enrolled at RP2D, and enrolment may be expanded up to approximately 40 patients if at least 3 pts with CR, PR or SD > 4 months per RECIST v1.1 or irRC are observed. In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criterion is met (Group 2b). The operating characteristics of the designs are provided in Table 3-1 (for Group 1, 3), Table 3-2 (for Group 4), and Table 3-3 (for Group 2 at RP2D), Table 3-4 (for Group 2b).

Table 3-1 Operating characteristics of the design (Group 1, 3)

True ORR	Probability to observe >=3 responses in first 20 patients	Group 1: TNBC Group 3: Endometrial cancer probability to observe an ORR ≥ 30% with 40 patients (Overall success rate)
15%	59.5%	1.2%
20%	79.4%	8.7%
25%	90.9%	28.4%
30%	96.5%	55.8%
40%	99.6%	92.8%
50%	100.0%	99.7%

Table 3-2 Operating characteristics of the design (Group 4)

True ORR	Probability to observe >=2 responses in first 20 patients	Groups 4: resistant melanoma probability to observe an ORR ≥ 15% with 40 patients (Overall success rate)
7.5%	44.9%	7.1%
15%	82.4%	54.2%
20%	93.1%	81.5%
30%	99.2%	98.6%
40%	99.9%	99.9%
50%	100.0%	100%

Table 3-3 Operating characteristics of the design (Group 2 at RP2D)

True CBR	Probability to observe >=3 responses (CR, PR or SD > 4 months) in first 20 patients	Group 2: Pancreatic cancer probability to observe a CBR ≥ 15% with 40 patients
7.5%	18.6%	5.5%
15%	59.5%	46.1%
20%	79.4%	73.4%
30%	96.5%	96.1%

Table 3-4 Operating characteristics of the design (Group 2b)

True CBR	Groups 2b: Pancreatic cancer probability to observe a CBR ≥ 15% with 20 patients
7.5%	18.6%
15%	59.5%
20%	79.4%
30%	96.5%

4 Change to protocol specified analyses

The following section have been updated in comparison to first SAP

Section 1.1 Study design

Section 1.2 Study objectives and endpoints

Section 2.1 Data analysis general information

Section 2.1.1 General definitions

Section 2.2 Analysis sets/Withdrawal of ICF/Subgroups

Section 2.4.1 Study treatment/compliance

Section 2.5.1 Primary endpoints

Section 2.5.2 Phase II part (Secondary endpoint)

Section 2.5.4 Supportive analyses

Section 2.7.1 Secondary endpoints

Section 2.8 Safety analyses

Section 2.8.3 Laboratory data[redacted]

Section 3 Sample size calculation

Section 5.5 Rule of exclusion criteria of analysis sets

Section 1.1 Study design

- Updated the study design for Phase II part per protocol amendment version 5

Section 1.2 Study objectives and endpoints

- Secondary objectives, Phase II part: changed endpoint for Group 2 (Pancreatic cancer) to CBR instead of ORR

Section 2.1 Data analysis general information

- Add R version which will be used for Bayesain anayses for Phase II part.

Section 2.1.1 General definitions

- Definition of on-treatment and post-treatment assessment/event

Section 2.2 Analysis sets/Withdrawal of ICF/Subgroups

- Per-protocol Set was planned as per the protocol, but outputs were not generated because no analyses were conducted based on per-protocol set
- Add section 2.2.5 Withdrawal of Informed Consent

Section 2.4.1 Study treatment/compliance

- Definition of last date of exposure of study drug/treatment (+ 20 days instead of + 21)

Section 2.5.1 Phase II part (Primary endpoint)

- Change of group 2 (Pancreatic cancer) endpoint to CBR instead of ORR

Section 2.5.2 Phase II part (Secondary endpoint)

- Change of group 2 prior distribution
- Update design of group 2 per protocol amendment version 5

Section 2.5.4 Supportive analyses

- Change to be not applicable cause supportive analyses were not conducted.

Section 2.7.1.2 Phase II (Secondary efficacy objectives)

- Group 2 (pancreatic cancer) secondary endpoint chnaged to CBR

Section 2.8 Safety analyses

- Definition of on-treatment period changed from including 90 days to 30 days after last dose in line with all other IO studies and reporting standards.
- Definition of post-treatment period changed from starting at day 91 after last dose of study medication to 31 days after last administration of study treatment in line with all other IO studies and reporting standards.

Section 2.8.3 Laboratory data

- Both fasting glucose and non-fasting glucose will be summarized and listed for information integrity. Both of glucoses will be combined and reported based on CTCAE v4.03. Fasting glucose values will be flagged in the listing.

Section 3 Sample size calculation

- Update study design for phase II part per protocol amendment version 5

Section 5.5 Rule of exclusion criteria of analysis sets

- Table for protocol deviations leading to exclusion from analysis set was removed due to no such PDs were collected

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

5.1.2 AE date imputation

A missing AE start date will be imputed using the following logic matrix described in Table 5-1.

Table 5-1 Imputation rules for a partially missing AE start date

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	No imputation	No imputation	No imputation	No imputation
AEY < TRTY	(D)	(C)	(C)	(C)
AEY = TRTY	(B)	(C)	(B)	(A)
AEY > TRTY	(E)	(A)	(A)	(A)

AEM: Month AE started; AEY: Year AE started
TRTM: Month treatment started; TRTY: Year treatment started

Table 5-2 is the legend to the logic matrix shown in Table 5-1 and details the relationship of AE start date to study treatment start date.

Table 5-2 Imputation legend and AE/treatment start date relationship

	AE start date relationship	Imputation
(A)	After treatment start or Uncertain	MAX(01MONYYYY, TRTSTD + 1)
(B)	Uncertain	TRTSTD + 1
(C)	Before treatment start	15MONYYYY
(D)	Before treatment start	01JULYYYY
(E)	After treatment start	01JANYYYY

Before treatment start: Partial date indicates AE start date is prior to treatment start date.
After treatment start: Partial date indicates AE start date is after treatment start date.
Uncertain: Partial date insufficient to determine relationship of AE start date to treatment start date.

No imputation will be performed for AE end dates.

5.1.3 Concomitant medication date imputation

Please refer to Section 5.1.2.

5.1.4 Prior therapies date imputation

Consider specific imputation rules for patial dates.

Start date:

The same rule which is applied to the imputation of AE/concomitant medication (Section 5.1.2) start date will be used with the exception that scenario (B) will be replaced to be ‘start date of study treatment - 1’.

End Date:

Imputed date = min (start date of study treatment, last day of the month), if day is missing;

Imputed date = min (start date of study treatment, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

5.1.5 Post therapies date imputation

If the day of the medication date is missing the following imputation rules will be followed:

- If the treatment end month and year and medication month and year are the same, then the day of the medication date is set to treatment end day + 1.
- If the month or year of the medication date is after the treatment end month/year then the day of the medication date set to the first of the month.

If the month of the medication date is missing the following imputation rules will be followed:

- If day is also missing,

- If the treatment end year and medication year are the same, then the month of the medication date is set to treatment end date + 1.
- If the year of the medication date is after the treatment end year then the month of medication date set to be 01-JAN.

- If day is not missing,
  - If the treatment end year and medication year are the same and if medication day is before the day of treatment end date, then the month of medication date is set to month of treatment end date + 1.
  - If the treatment end year and medication year are the same and if medication day is after the day of treatment end date, then the month of medication date is set to month of treatment end date.
  - If the year of the medication date is after the treatment end year then medication date set to be JAN.

If the year of the medication date is missing there is no imputation.

5.1.6 Other imputations

For partially missing date of first recurrence/progression, date of initial diagnosis or date of most recent relapse/progression the following imputation rules will be applied:

- If Month and Day missing, set to 01-Jul of the year
- If Day missing, set to 15 of the month

5.2 Laboratory parameters derivations

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium as defined in the previous section.

5.3 Rule of exclusion criteria of analysis sets

Patients will be excluded from the analysis sets based on the protocol deviations entered in the database and specific non-protocol deviations. All protocol deviations and non-protocol deviations leading to exclusion from specific analysis sets will be finalized before database lock.

Table 5-3 displays non-protocol deviations leading to exclusion from analysis set definitions These table will be updated before database lock.

Table 5-3 Non-protocol deviations leading to exclusion from analysis set definitions

Summary of non PD	Analysis set(s) to be excluded
No post-baseline safety assessment	SS
1. Patient, who has not experienced DLT, was not observed for ≥ 42 days following the first dose or had not completed the required safety evaluations for Cycle 1 and Cycle 2 or 2. Patient who has not experienced DLT, didn't receive two doses in the first two cycles.	DDS
Patient did not have at least one primary PK parameter	PAS

6 Reference

Neuenschwander B, Branson M, and Gsponer T (2008). Critical aspects of the Bayesian approach to phase I cancer trials. Statistics in Medicine 27: 2420-2439.

Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian Approaches to Clinical Trials and Health-Care Evaluation. John Wiley & Sons, New York, 2004.

Neuenschwander B, Capkun-Niggli G, Branson M, Spiegelhalter D (2010) Summarizing historical information on controls in clinical trials. Clin Trials 2010 7: 5.

Neuenschwander B, Matano A, Tang Z, Roychoudhury S, Wandel S and Bailey S: A Bayesian Industry Approach to Phase I Combination Trials in Oncology in Zhao W and Yang H. Statistical Methods in Drug Combination Studies. Chapman & Hall/CRC, 2014.

Rogatko A, Schoeneck D, Jonas W, et al (2007) Translation of innovative designs into phase I trials. J Clin Oncol; 25(31): 4982-6.