NOVARTIS

Clinical Development

MCS110

CMCS110Z2201 / NCT02435680

A randomized phase II study of MCS110 combined with carboplatin and gemcitabine in advanced Triple Negative Breast Cancer (TNBC)

Statistical Analysis Plan (SAP)

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23-Aug-2016	Prior to LPFV	Creation of final version	N/A - First version	NA
20-Oct-2018	after enrollment halt	Enrollment Halt	Amendment 1	1.1 Study design 1.2 Study objectives and endpoints 2.5 Analysis of primary objective 2.6 Analysis of the key secondary objective 2.8 Safety analyses 2.9 Pharmacokinetic endpoints: 2.10 Biomarkers

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BDM	Biometrics and Data Management
CR	Complete response
CRO	Contract Research Organization
CSF-1	Colony stimulation factor – 1, also called M-CSF
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTX-I	C-terminal telopeptide of type I collagen, a bone reabsorption marker
DAR	Dose administration record
DBL	Database lock
DI	Dose intensity
DMC	Data Monitoring Committee
DOR	Duration of response
DRI	Drug reference listing
ECG	Electrocardiogram
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HR	Hazard ratio
IHC	Immunohistochemistry
INR	International normalized ratio
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantificaton
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall respolnse rate
OS	Overall Survival
PD	Pharmacodynamics
PDI	Planned dose intensity
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial response
PRO	Patient-reported Outcomes
QoL	Quality of Life
RAP	Report and Analysis Process

RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International System of Units
SOC	System Organ Class
SSD	Study specification document
TAM	Tumor-associated macrophages
TFLs	Tables, Figures, Listings
TIL	Tumor-infiltrating lymphocytes
TNBC	Triple Negative Breast Cancer
ULN	Upper Limit of Normal
WHO	World Health Organization

1 Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CMCS110Z2201 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 the clinical 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.

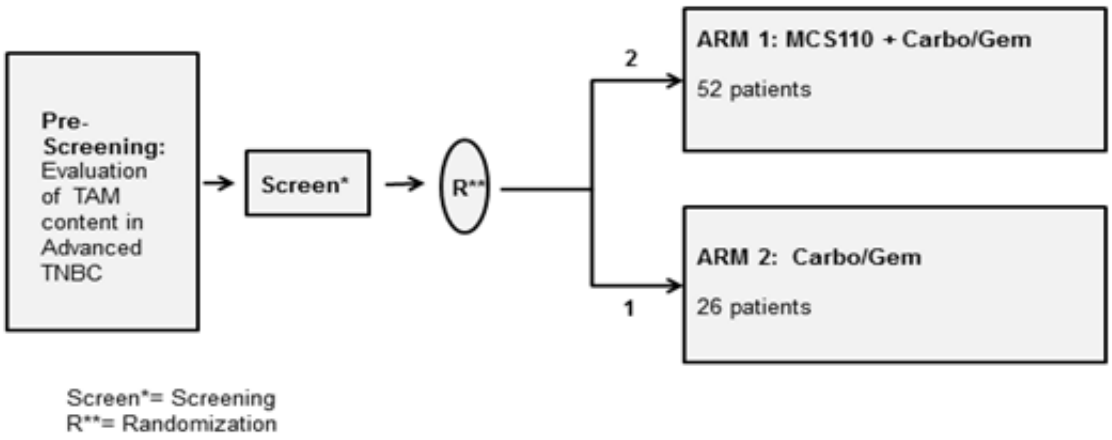
The SAP, TFL shells and PDS documents may also serve as a reference for the creation of any outputs required outside of the CSR, e.g., IB updates, abstracts, posters, presentations, manuscripts and management updates. Data used for these analyses will have a status aligned to the database lock guidance.

This document uses CMCS110Z2201 study protocol version 06 as a reference. Novartis has halted the recuitment of the study as of June 16th, 2017 due to challenging enrollment and rapid evolution of the therapeutic landscape. Importantly, the recruitment halt was not a consequence of any safety concern. The changes to the protocol planned statistical analyses and to the original SAP are described in Section 4.

1.1 Study design

This is a phase II, randomized (2:1), two-arm, open-label multi-center, study of patients with advanced TNBC. As shown in Figure 1-1, patients will be randomized in a ratio of 2:1 to Arm 1 (MCS110 + carbo/gem) and Arm 2 (carbo/gem). No stratification factor will be used.

Figure 1-1 Overview of study design



An early safety review meeting will take place when nine patients have been randomized and completed two cycles of either MCS110 + carbo/gem or carbo/gem alone, or discontinued earlier due to adverse event. If the dosing regimen is changed at this time, an additional safety review of the new dosing regimen will take place after six patients have been randomized and

completed two cycles of MCS110 (per the new dosing regimen) + carbo/gem, or discontinued earlier due to an adverse event. Any subsequent MCS110 changes of the dosing regimen will be followed by an additional safety review per the procedure just described.

Novartis clinical team and principal investigators will assess clinical, PK and laboratory data of all patients having received any treatment in the study before each of the meeting(s) to decide on the subsequent MCS110 dose regimen. One of the following dosing alternatives will be chosen:

- If no safety concerns are noted during the safety review and the observed drug exposure is within that observed in cynomolgus monkeys and/or HV (clinical study protocol (CSP) Table 2-1), then the same MCS110 dose will be continued.
- If safety concerns are noted, then the MCS110 dose will be reduced (from 10 mg/kg to 5mg/kg, or from 5 mg/kg to 2.5 mg/kg) and the additional dose of MCS110 on C1D8 may be omitted, after review with the Steering Committee.

Once a dosing regimen is agreed upon after the safety review meeting(s), all the subsequent patients randomized to Arm 1 will receive the confirmed dose. The study will continue until 52 patients have been randomized to Arm 1 and treated at the dose level confirmed as the final recommended dose for MCS110 combined with carbo/gem.

If there is no change to the MCS110 dosing regimen following the first safety review meeting, the total number of patients for this study will be 78. If the dosing regimen is changed, the total number of patients for the study may be approximately 110, as recruitment will continue during the decision making.

After the early safety review(s), individual patient data will subsequently be reviewed on an ongoing basis and discussed with Investigators throughout the duration of the trial. Aggregate safety data and the primary endpoint will be monitored quarterly by the study team. This data monitoring will be based on the available data in the clinical database at the respective time.

The primary efficacy endpoint, progression free survival (PFS) as determined through the local Investigator's tumor assessment per RECIST 1.1, will be analyzed according to the study arm patients are randomized to. Due to enrollment halt, formal hypothesis testing for the primary analysis including HR estimation with 90% credible interval will not be carried out for the CSR. Only Kaplan-Mayer (KM) curve between the MCS110 + carboplatin/gemcitabine arm and the carboplatin/gemcitabine alone arm will be presented. The analysis of the study data for the CSR will be done in one of the following approaches:

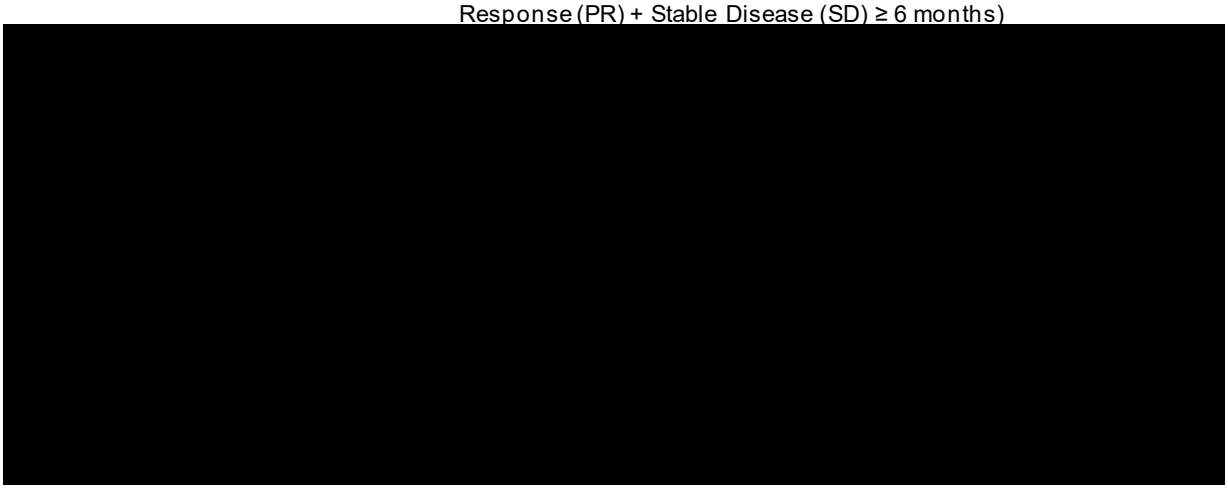
- The CSR will be based on all patients' data at the end of the study, or
- The study data will be analyzed and reported in the primary CSR based on all patients' data up to the time when all patients have completed at least six cycles of treatment or discontinued the study. Any additional data for patients continuing to receive study treatment past the data cutoff date for the primary CSR, as allowed by the protocol, will be reported once end of study has been achieved.

1.2 Study objectives and endpoints

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

Table 1-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		
To assess the anti-tumor activity of MCS110 combined with carboplatin/gemcitabine (carbo/gem) compared to carbo/gem alone	PFS as per RECIST v1.1 (by local investigator assessment)	Refer to Section 2.5
Secondary		
Characterize the safety and tolerability of MCS110 given in combination with carbo/gem	Safety: adverse event (AEs), serious adverse events (SAEs) Tolerability: Dose interruptions, reductions and dose intensity	Refer to Section 2.8
Characterize PK of MCS110 when combined with carbo/gem	Serum concentration of free MCS110 and derived PK parameters	Refer to Section 2.9
Characterize PK of carbo and gem in the presence and absence of MCS110.	Plasma concentration of carboplatin, gemcitabine and dFdU (the primary metabolite of gem), and derived PK parameters	Refer to Section 2.9
Characterize PD effect of MCS110 when combined with carbo/gem	Total CSF-I circulating levels, and serum CTX-I in blood. TAM and TIL content in pre- and post-dose tumor biopsies	Refer to Section 2.10
To assess the anti-tumor activity of MCS110 given in combination with carbo/gem as measured by additional efficacy measures	Tumor response per RECIST v1.1 (by local investigator assessment): Overall Response Rate (ORR), Duration of Response (DOR), and Clinical Benefit Rate (Complete Response (CR) + Partial Response (PR) + Stable Disease (SD) ≥ 6 months)	Refer to Section 2.7



2 Statistical methods

This section and its subsections can be imported to section 9.7 of the CSR after the analyses have been conducted. The text will be changed to the past tense when imported into the CSR.

2.1 Data analysis general information

The data will be analyzed by Novartis personnel and/or designated CRO(s) using SAS version 9.4, and for Bayesian modeling, R version 3.0.2 or later and WinBUGS14. PK parameters will be calculated using non-compartmental methods available in Pharsight Phoenix version 6.4.

The study data will be analyzed and reported (in a primary CSR if final DBL has not occurred) based on all patient data either at the end of the study or up to the time when all patients have completed at least six cycles of treatment or discontinued the study. Additional data for patients continuing to receive study treatment past the data cutoff date of the primary CSR, as allowed by the protocol, will be reported in the final CSR once all patients have either completed or discontinued the study. However, only a selection of key outputs (indicated in the TFL shells document) will be provided for the final CSR.

Data from participating centers in this study protocol will be combined, so that an adequate number of patients will be available for analysis. No center effect will be assessed. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic (PK) and pharmacodynamics (PD) measurements using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) for quantitative data and contingency tables (frequencies and percentages) for qualitative data.

2.1.1 General definitions

Study drug and study treatment

The investigational drug refers to MCS110, the Novartis anti-CSF-1 recombinant humanized monoclonal antibody. The investigational treatment refers to carbo/gem with or without MCS110.

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

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. For the sake of simplicity, the date of first (last) administration of study treatment will also be referred as start (last) date of study treatment.

Study day

The study day for all assessments/events will be calculated using the date of randomization as reference for FAS or the start date of study treatment as reference for all other analysis sets. 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.

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 + 30 days inclusive.

2.2 Analysis sets

The number (%) of patients in each of the defined analysis set will be summarized using the FAS.

Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intention to treat principle, patients will be analyzed according to the treatment to which they have been assigned during the randomization procedure.

Unless otherwise specified the FAS will be the default analysis set used for all analyses and listing of raw data.

Safety Set

The safety set includes all patients who received at least one dose of MCS110 or carboplatin or gemcitabine for Arm 1, at least one dose of carboplatin or gemcitabine for Arm 2. The statement that a patient had no AEs (on the AE eCRF) constitutes a valid safety assessment.

Patients will be classified according to treatment received, where treatment received is defined as:

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

The safety set will be the primary population for all safety related endpoints.

Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have an evaluable pharmacokinetic (PK) profile (e.g., Cycle 1, Cycle 4, etc). A profile is considered evaluable if all of the following conditions are satisfied:

- Patient receives the planned treatment on the profile day
- Patient provides at least one primary PK parameter

The PAS will be used for summaries of PK concentration data, PK parameters [redacted]. Patients will be analyzed according to the planned treatment. Patients may be removed from PK analysis on an individual basis depending on the number of available blood samples. These patients will be identified at the time of analysis.

2.3 Patient disposition, demographics and other baseline characteristics

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 randomized patients who are treated and who are untreated,
- 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 and reason 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 and reason entered),
- Primary reasons for post-treatment follow-up discontinuation (based on discontinuation reason entered in the 'End of Post Treatment Phase Disposition' page).

2.3.2 Basic demographic and background data

Demographic data including age, predominant race, ethnicity, height, weight and ECOG performance status will be listed and summarized by study arm and treatment group. In addition, child bearing potential will be listed, and age (<65, 65-<85, ≥85 years) category summarized.

2.3.3 Medical history

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

2.3.4 Prior antineoplastic therapy

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

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

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, time (in days) between end of last medication to start of study treatment, and reason for discontinuation at last medication. 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 and procedure at last surgery.

2.3.5 Diagnosis and extent of cancer

The summary and listing of diagnosis and extent of cancer (disease history) will include primary site of cancer, details of tumor histology/cytology, histological grade, stage at initial diagnosis, time (in months) from initial diagnosis of primary site to start of study treatment, time (in months) from 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), BRCA1 mutation, and BRCA2 mutation.

2.3.6 Protocol deviations

The FAS will be used for the protocol deviation summary tables and listings. The number (%) of patients with any CSR-reportable protocol deviation will be tabulated by the deviation category (entry criteria not satisfied; wrong treatment or incorrect dose; developed withdrawal criteria, but not withdrawn; took an excluded concomitant medication; others). The full list of protocol deviations are documented in the Study Specification Document (SSD). Protocol deviations leading to exclusion from analysis sets are specified in Section 5.7.

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

2.4.1.1 Study treatment

Last date of exposure to study drug MCS110 = last date of administration of MCS110 + 20 days

Last date of exposure to study drug carbo = last date of administration of carbo + 20 days

Last date of exposure to study drug gem = last date of administration of gem + 20 days

Last date of exposure to study treatment is the maximum of the last date of exposure to each study drug.

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

Dose administered (AUC2) for carbo = Dose prescribed (AUC2) * Total volume administered (mL) / Total volume planned to be administered (mL)

Dose administered (mg/m^2) for gem = Dose prescribed (mg/m^2) * Total volume administered (mL) / Total volume planned to be administered (mL)

Planned dose is the dose level of a study drug assigned during randomization.

Definitions of duration of exposure, cumulative dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), percentage of cycles the planned/intended dose was received, as well as intermediate calculations, are as follows:

- Duration of exposure (days) to study drug/treatment: last date of exposure to study drug/treatment − first date of study drug/treatment + 1 (periods of interruption are not excluded)
- Cumulative dose (mg/kg for MCS110, mg/m^2 for gem, AUC2 for carbo): sum of all doses of study drug taken by a patient
- Cumulative planned dose (mg/kg for MCS110, mg/m^2 for gem, AUC2 for carbo): sum of all doses of study drug that was intended to have been taken during the treated period by a patient
- Percentage of cycles at planned dose: 100 × number of cycles at planned dose/number of cycles scheduled per protocol during treatment period
- DI (mg/kg for MCS110, mg/m^2 for gem, AUC2 for carbo): cumulative dose (mg/kg for MCS110, mg/m^2 for gem, AUC2 for carbo)/planned number of doses patient should have taken
- PDI (mg/kg for MCS110, mg/m^2 for gem, AUC2 for carbo): cumulative planned dose (mg/kg for MCS110, mg/m^2 for gem, AUC2 for carbo)/planned number of doses patient should have taken
- RDI (%): 100 × DI /PDI

All the above variables will be calculated for MCS110, carboplatin and gemcitabine separately.

The duration of exposure to each 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. 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.

Dose interruption: If a dose is given more than 6 days after the scheduled day of dosing, it is considered a dose interruption.

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, where treatment received is defined in Section 2.2.

2.4.1.2 Compliance

Compliance to the study treatment within each study arm/treatment group will be assessed by the number of dose reductions, number of dose interruptions and percent of cycles received planned dose for all the study drugs separately in summary tables by study arm and treatment group for the safety set.

2.4.2 Prior, concomitant and post therapies

Concomitant therapies are defined as any medications (excluding study treatment, prior 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. These summaries will include 1) medications or therapies starting on or after the start of study treatment but starting no later than 90 days after last dose of study treatment and 2) medications or therapies starting prior to the first dose of study treatment and continuing after the start of study treatment.

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.4.3 for more details). No imputation will be performed for concomitant medication end dates.

Anti-neoplastic therapies since discontinuation of study drug will be listed.

2.5 Analysis of the primary objective

The primary objective is to assess the anti-tumor activity of MCS110 combined with carboplatin/gemcitabine compared to carboplatin/gemcitabine in adult patients with triple negative breast cancer.

2.5.1 Primary endpoint

The primary efficacy endpoint is progression-free survival (PFS) based on local Investigator assessment, as defined in RECIST v1.1. PFS is defined as the time from the date of randomization to the date of the first radiologically documented PD or death due to any cause. Due to enrollment halt, formal hypothesis testing for the primary endpoint including hazard ratio for PFS with 90% credible interval between the MCS110 + carbo/gem arm and the carbo/gem arm (as detailed out in Section 2.5.2) will not be carried out. Only Kaplan-Meier curve by treatment arms will be presented.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint, PFS as determined through the local Investigator's tumor assessment per RECIST 1.1, will be analyzed according to the study arm patients are randomized to. However, due to enrollment halt, formal hypothesis testing as sepcified below

including estimation of HR and 90% confidence interval will not be carried out. PFS will be presented graphically using Kaplan-Meier plots for both the MCS110 + carboplatin/gemcitabine arm and the carboplatin/gemcitabine arm.

The primary analysis of the study is based on the estimation of the hazard ratio between the MCS110 + carboplatin/gemcitabine arm and the carboplatin/gemcitabine alone arm and related one-sided 90% credible interval of the HR.

The following double criteria will be used in order to conclude that there is clinical and statistical evidence of efficacy of the MCS110 + carboplatin/gemcitabine combination treatment compared to the carboplatin/gemcitabine alone treatment:

- the estimated hazard ratio (posterior median) is equal or less than 0.7 (i.e 30% reduction in risk of PFS event with MCS110 + carboplatin/gemcitabine arm compared to the carboplatin/gemcitabine arm),
- the upper bound of the one-sided 90% credible interval of the HR is below 1.

Estimated HR for the MCS110 + carboplatin/gemcitabine arm compared to the carboplatin/gemcitabine arm along with the one-sided 90% confidence interval will be produced

2.5.3 Handling of missing values/censoring/discontinuations

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier, as defined in the in the RECIST v1.1 (CSP Appendix 1). Clinical deterioration will not be considered as a qualifying event for progression.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurs after a new anticancer therapy is given; the event occurred after two or more missing tumor assessments. Any response assessment is considered to be adequate if the assessment was perfomed and the outcome of the assessment was other than ‘unknown’.

Patients without baseline tumor assessment or any tumor assessment after the start date of study treatment will be censored at the date of randomization in the primary analysis, but will be excluded in the PPS for sensitivity analysis, if performed.

2.5.4 Supportive analyses

NA

2.6 Analysis of the key secondary objective

NA

2.7 Analysis of secondary efficacy objective(s)

ORR is defined as the proportion of patients with a best overall resonse of complete response (CR) or partial response (PR) per RECIST v1.1.

CBR is defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) or stable disease (SD) ≥ 6 months per RECIST v1.1.

Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response. BOR for each patient is determined from the sequence of overall lesion responses according to the following rules:

• CR = at least two determinations of CR at least 4 weeks apart before progression.

• PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).

• SD = at least one SD assessment (or better) > 5 weeks after start of treatment (and not qualifying for CR or PR).

• PD = progression ≤ 12 weeks after start of treatment (and not qualifying for CR, PR or SD).

• UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or progression within the first 12 weeks)

Unconfirmed PR and unconfirmed CR are considered as stable disease (SD) if > 5 weeks after start of treatment, otherwise considered as unknown. Patients who are of unknown clinical response or have no post-baseline tumor assessment will be treated as non-responders.

Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e., any additional secondary anti-neoplastic therapy or anti-cancer surgery) will be considered in the assessment of BOR. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on 'Anti-neoplastic therapies since discontinuation of study drug' as appropriate. Clinical deterioration will not be considered as documented disease progression.

The best overall response will usually be determined from response assessments undertaken while on treatment. As a default, any assessments taken more than 90 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 assessments would be excluded from the best overall response determination.

Individual lesion measurements will be listed along with the overall lesion response and Best Overall response (BOR).

Among patients with a confirmed PR or CR per RECIST 1.1, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression (PD) or death due to any cause. If a patient has not had an event, DOR is censored in the same way as PFS, at the date of last adequate tumor assessment.

DOR will be presented descriptively using Kaplan Meier plots for the two study arms. In addition, the median DOR will be presented.

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.

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 medication,
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication,
3. Post-treatment period: starting at Day 31 after last dose of study medication.

The safety summary tables will primarily be based on all data from the on-treatment period, which is collected no later than 30 days after study treatment discontinuation. However, in the listings all safety assessments will be listed and those collected after study treatment discontinuation will be flagged.

2.8.1 Adverse events (AEs)

AEs 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.

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.

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 suspected to be study drug related leading to discontinuation of study drug
- AEs regardless of study drug relationship requiring dose adjustment or study drug interruption
- AEs suspected to be study drug related requiring dose adjustment or study drug interruption
- AEs which are not SAEs regardless of study drug relationship
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related

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).

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment-emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population. This analysis will be done after the final database lock.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

All deaths will be listed, with post-treatment deaths flagged. The following summaries of deaths will be produced:

- On-treatment deaths with cause of death by preferred term
- 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 statistical programming) into CTC grades according to CTCAE v4.03. Grade 5 will not be used.

Change from baseline criteria will not be used in derivation of CTC grade. A Grade 0 CTC grade will be set when laboratory value is:

- Within LLN and ULN and grading in both direction,
- Below ULN and grading in hyper direction,
- Above LLN and grading in hypo direction.

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 biochemistry parameters:

- For parameters with CTC grades: Shifts from baseline to the worst post-baseline CTC grade (Each patient will be counted only for the worst grade observed post-baseline.)
- For parameters with no CTC grades defined: Shifts from baseline to the worst post-baseline using low/normal/high classifications, based on laboratory normal ranges

The following listings will be produced:

- Listing of patients with laboratory abnormalities of CTC grade 3 and 4
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades if applicable and the classifications relative to the laboratory normal ranges

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

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

Hematology and coagulation		Biochemistry	
White Blood Cells (WBC)	↑↓	Creatinine	↑
Hemoglobin	↑↓	Sodium	↑↓
Platelets	↓	Potassium	↑↓
Absolute Neutrophils	↓	Calcium	↑↓
Absolute Lymphocytes	↑↓	Alkaline phosphatase	↑
International normalized ratio (INR)	↑	Albumin	↓
		AST (SGOT)	↑
		ALT (SGPT)	↑
		Bicarbonate	↓
		Total Bilirubin	↑
		Creatine kinase (CK)	↑
		Uric Acid	↑
		Blood plasma Glucose	↑↓
		Phosphate	↓

↑ 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
Prothrombin time (PT)	Blood urea nitrogen (BUN)
	Urea

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.

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

- Number (%) of patients having notable ECG values according to Table 2-3.

Table 2-3 Criteria for notable ECG values

ECG parameter	Criteria for notable ECG values
QT, QTcF, QTcB (ms)	New value of > 450 ms, > 480 ms, > 500 ms Increase from baseline of > 30 ms, > 60 ms
HR (bpm)	Increase from baseline > 25% and to a value > 100 bpm Decrease from baseline > 25% and to a value < 50 bpm
PR (ms)	Increase from baseline > 25% and to a value > 200 ms New value of > 200 ms
QRS (ms)	Increase from baseline > 25% and to a value > 120 ms New value of > 120 ms

Patients with any notable ECG values will be listed.

2.8.4.2 Vital signs

Vital sign parameters collected are systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), respiratory rate (breaths 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

Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced.

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

2.9 Pharmacokinetic endpoints

All PK analyses will be performed based on the PAS. Only PK blood samples with the date and time and for which the last prior dose dates and times are adequately recorded will be included in the PK analyses. Missing concentration values will be reported as is in data listings. Concentration values below Lower limit of quantitation (LLOQ: 20 ng/mL for free MCS110; 1.5 ng/mL for total CSF-1; 2 ng/mL for carboplatin; 0.5 ng/mL for gemcitabine; and 5 ng/mL for dFdU) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

PK parameters will be calculated using noncompartmental methods and summarized as described in Table 2-5. The PK parameters considerd primary are AUCinf, AUCtau, AUClast, Cmax, and Tmax. Other PK parameters (CL, Vz, T1/2) are considered as secondary.

Table 2-5 PK parameters – descriptive statistics

Parameters	Descriptive statistics
AUCinf, AUCtau, AUClast, Cmax, Tmax, CL, Vz and T1/2	Mean, standard deviation, CV% mean, geometric mean, CV% geometric mean, median, minimum and maximum
CV% = coefficient of variation (%) = sd/mean*100 CV% geometic mean = sqrt (exp (variance for log transformed data)-1)*100	

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all parameters by analyte, study arm and study cycle/day. When a geometric mean is presented, it will be stated as such. Zero concentrations will not be included in the geometric mean calculation. Since Tmax and T1/2 are generally evaluated by a nonparametric method, median values and ranges will be presented for these parameters. All primary PK parameters will be listed. [redacted]

Descriptive graphical plots of individual and mean serum/plasma concentration versus time profiles of free MCS110, total CSF-1 and other PD biomarkers (e.g. CTX-1, and monocytes) will be generated.

2.10 Biomarkers

2.10.1 Introduction

As a project standard, Novartis biostatistics and statistical programming will analyze only biomarkers collected in the clinical database. [redacted]

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of blood / archival tumor samples / fresh tumor biopsies / fine needle aspirates due to either practical or strategic reasons (e.g. issues related to the quality and/or quantity of the samples or issues related to the assay). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed and potentially summarized.

2.10.2 Outline of the data analysis

Additional analyses that may be performed after the completion of the final (end-of-study) CSR will be documented in separate reports. These analyses may include but are not limited to the meta-analysis of data from this study combined with data from other studies or the analysis of

biomarkers generated from samples collected during the study but analyzed after the database lock and completion of the CSR. The data analysis will be described in an addendum of the SAP or in a stand-alone analysis plan document, as appropriate.

[redacted]

Only analysis specified in the secondary objectives may be performed and reported depending on the quality and/or quantity of the samples collected.

2.10.3 Biomarker objectives

The biomarker objectives and corresponding endpoints are described in Section 1.2.

2.10.4 Biomarker analysis data set

The Full Analysis Set will be used for all biomarker analysis. Unless otherwise specified, all statistical analyses of biomarker data will be performed on patients with biomarker data.

Assessment of associations between biomarker and safety data will be conducted using the Safety Set.

2.10.4.1 List of biomarkers evaluated and the collection time points

Table 2-6 Sample biomarker summary table

Sample Type	Visit/Time point	Volume	Marker	Purpose	Method	Data set
Tumor samples						
Newly obtained tumor sample	Pre-screening	FFPE tumor block/freshly-cut sections of newly obtained biopsy or 3-6 passes of newly obtained tumor biopsy	CD163 expression	Patient selection and PD marker To determine TAM content	Immunohistochemistry	IHC
Newly obtained tumor sample	Screening * Between C2D8 and C3D1 **	FFPE tumor block/freshly-cut sections of newly obtained biopsy or 3-6 passes of newly obtained tumor biopsy	CD8, CD163 [redacted]	[redacted] To evaluate CD163+ TAMs as a PD marker To evaluate whether specific immune populations (CD8+ TILs) [redacted]	Immunohistochemistry [redacted]	IHC [redacted]

Sample Type	Visit/Time point	Volume	Marker	Purpose	Method	Data set
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Blood samples						
Blood serum	Pre-dose sample: C1D1 pre-dose and C1D2, C1D4, C1D8, C1D15, C2-8D1	6 mL (minimum)	CTX-I [redacted]	[redacted] To evaluate bone resorption [redacted]	ELISA/MSD (Meso Scale Discovery)	MSD
[redacted]						

* Using remaining tissue from newly obtained pre-screening tumor biopsy
** If obtaining of the biopsy is not medically feasible between C2D8 and C3D1, the biopsy may be collected at a later time point at the investigator's discretion.
*** Not required if tumor sample from the initial diagnosis is used as the newly obtained tumor sample.
Note 1: On days and time points when biomarker and pharmacokinetic blood samples are being collected, the PK sample must be drawn first.
[redacted]

2.10.4.2 Data handling principles

All measurements below their respective LLOQs or missing data will be labeled as such in the concentration data listings. Measurements below the LLOQ will be treated as zero in summary statistics. Change from baseline analyses will only be performed on patients with measurable samples and pre- and post-treatment time points.

2.10.4.3 Data analysis principles

2.10.4.3.1 Analysis sets

The FAS will be used for all analyses. Patients with measureable tumor samples will be identified in the summaries and relevant proportions will be calculated against this number of patients.

2.10.4.3.2 Basic tables, figures and listings

[redacted]

Assessment of pharmacodynamic biomarkers

The extent of TAM suppression and TIL increase will be assessed by IHC in pre- and post-treatment formalin-fixed paraffin embedded tissue obtained during the study, when feasible. For this purpose, the TAM and TIL content will be compared with baseline levels by producing a summary table with the descriptive statistics. Data will also be listed by patient for all these markers. [redacted] Furthermore, the PD effect of MCS110 when combined with carboplatin/gemcitabine will also be characterized by assessing the total CSF-1 circulating levels, serum CTX-1 and circulating monocytes in blood. Both summary statistics and listings will be produced.

2.10.4.3.3 Advanced analysis methods

A logistic regression model will be used to determine whether the baseline mutation status (e.g. BRCA), protein expression levels (e.g. S-CSF-1 levels), cell content (e.g. TAM levels, TIL levels) are potentially correlated with clinical response to the combination of MCS110 and carboplatin/gemcitabine. Kaplan-Meier estimates of PFS by mutational status and treatment will also be produced.

2.11 Other Exploratory analyses

There are no other exploratory analyses planned.

2.12 Interim analysis

When the first 9 patients randomized in the study have completed two cycles of treatment or discontinue earlier due to adverse event, Novartis and principal investigators will have a safety review meeting to review clinical, PK and laboratory data and to decide on the dose for study continuation (CSP Section 2.2 and Section 4.1). If the monitoring of the study data requires a decision to be taken on the continuation of the study, then the relevant data will be communicated to the Steering Committee (CSP Section 8.5).

Outputs to be produced for the safety review has been identified in a separate RAP document (MCS110Z2201 Steering Committee Charter and Interim Analysis RAP).

Efficacy and safety data will be reviewed on a regular basis as mentioned in CSP Section 8.5. This data monitoring will not constitute a formal interim analysis of the primary endpoint since no decision to stop the study early will be taken following the review of this data.

Analyses produced for this review will include:

1. Analysis of primary efficacy endpoint
2. The following safety summaries and listings:
   - Treatment-emergent AEs regardless of study drug relationship
   - AEs leading to permanent discontinuation of study drug
   - AEs requiring dose adjustment or study drug interruption
   - SAEs regardless of study drug relationship
3. Summaries of key baseline characteristics

3 Sample size calculation

For this trial, information currently available coming from O'Shaughnessy 2011 for carboplatin/gemcitabine (see CSP Section 1.1) has been used in order to set up the criteria which will need to be satisfied to consider a clinically relevant efficacy of the MCS110 + carboplatin/gemcitabine combination treatment compared to the carboplatin/gemcitabine alone treatment. An estimation of at least 30% reduction in risk of PFS event with MCS110 + carboplatin/gemcitabine compared to the carboplatin/gemcitabine alone arm, or correspondingly, an estimated PFS HR $\leq$ 0.7 would be considered as clinically relevant. Besides, it would be considered as statistical significant if the upper bound of the one-sided 90% CI of the HR is below 1. As mentioned in CSP Section 10.4.2, this double criteria will be used in order to conclude that there is clinical and statistical evidence of efficacy of the MCS110 + carbo/gem combination treatment compared to the carbo/gem alone treatment.

Under the assumption that subject accrual (entry) occurs in the first 14 months, the study lasts for 22 months with an uniform accrual pattern across months (all periods equal) and the dropout rate with the assumption of censoring at time 0 being equal to 10%, it is estimated that a one-sided logrank test with a type-1 error equal to 10%, with approximately 58 PFS events and an overall sample size of 78 patients (52 in the MCS110 + carboplatin/gemcitabine arm and 26 in the carboplatin/gemcitabine alone arm) achieves the results presented in the following Table 3-1.

Table 3-1 True PFS hazard ratio and corresponding power

True hazard ratio (Alternative hypothesis)	Probability of concluding efficacy (power)
0.4	98%
0.5	90%
0.6	72%
0.7	50%
1.0	9%

The analysis has been performed with PASS 2008 and R-project 2.13.2.

4 Change to protocol specified analyses

As a result, the primary objective, to assess the anti-tumor activity of MCS110 combined with carboplatin and gemcitabine (carbo/gem), will not be reached. Therefore, the formal hypothesis testing including estimation of HR and 90% credit interval will not be performed. Analysis of OS will be removed. [redacted] Only summary tables and listings of PK endpoints and biomarkers will be presented.

The following section have been updated in comparison to first SAP

Section 2.1.1 General definitions

- Definition of on-treatment assessment/event

Section 2.5 Analysis of the primary objective

- Formal hypothesis testing of the primary objective will not be performed. HR and 90% credit interval will not be presented. Only K-M curve will be produced by treatment arms(MCS110 + carbo/gem VS. carbo/gem only).

Section 2.6 Analysis of the key secondary objective

- OS will not be analyzed due to removal of survival follow-up.

Section 2.8 Safety analyses

- Defintion 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.

[redacted]

- [redacted]

Section 2.10 Biomarkers

- [redacted]
- Advanced analysis such as logistic regression model will not be applied.

Section 2.12 No interim analysis will be carried out.

5 Appendix

5.1 Baseline

Baseline is the last available and valid assessment performed or value measured within 28 days 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, samples for biomarkers).

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.

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

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

5.2 Handling of missing and partial dates

For patients not known to have died prior to the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing at the cut-off date. For these events, the end date will not be imputed.

For patients known to have died prior to or on the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the date of death. For these events, the imputed end date will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed to the cut-off date in order to calculate e.g., the duration of exposure to study treatment. The imputed date will be displayed and flagged in the listings.

5.3 Construction of waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient.

Note: Patients without any valid assessments to calculate a percentage change from baseline value will be excluded from the graphs. Assessments with an unknown overall response will be included as long as the sum of diameters of target lesions is correctly computed on the same lesions assessed at baseline.

Patients will be ordered in the graph from left (worst change) to right (best change).

1. Bars above the horizontal axis (0%) representing tumor growth,

2. Bars under the horizontal axis (0%) representing tumor shrinkage.

A special symbol (e.g. $*$) will be added below the bottom of respective bars for confirmed RECIST response (CR or PR), with corresponding specificatons in footnote. The total number of patients displayed in the graph (n) over the total number of patients in the FAS (N) will be

shown. The best overall response (BOR) will be shown above each of the displayed bars in the graph. Symbols will be used to differentiate groups of interest, i.e. study arm. A horizontal threshold line at -30% will be shown.

5.4 Imputation rules

5.4.1 Study drug

Dose administration record with missing or partial dates are not acceptable, and should always be queried. The start and end dates for each DAR are expected to be the same.

5.4.2 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	01MONYYYY
(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.

5.4.3 Medication/therapy date imputation

5.4.3.1 Prior antineoplastic therapy date imputation

The imputation of a prior therapy start date will follow the same conventions as for an AE start date (see Section 5.4.2 AE date imputation), with the exception that scenario (B) will be replaced to be 'Start date of study treatment – 1'.

For missing end date imputation:

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

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

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

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

5.4.3.2 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.4.2 AE date imputation). No imputation will be performed for concomitant medication end dates.

5.4.3.3 Post antineoplastic therapy date imputation

Post therapies date imputation should not have to be considered. Any data entered in the eCRF pages are considered as starting after the last treatment, after being queried and verified.

5.5 Laboratory parameters derivations

Serum creatinine clearance is derived according to the Cockcroft-Gault equation: (140-age (years)) × weight (kg) (× 1.04 if female) / (serum creatinine (umol/L)).

Corrected Calcium (mg/dL) = 0.8 × (Normal Albumin (g/dL) – Albumin (g/dL)) + Serum Calcium (mg/dL), where normal albumin is 4 g/dL.

5.6 Statistical models

5.6.1 Primary analysis

In the following, the statistical model and prior distributions for the Bayesian Cox proportional hazard (PH) model will be described. We consider here the use of historical data of the same patient population to enrich the chemo arm (Arm 2).

5.6.1.1 Model Specification

The primary analysis of progression free survival (PFS) will be based on a Bayesian Cox PH model. This model will be used to estimate the hazard ratio for PFS of Arm 1 vs. Arm 2. This model assumes that the hazard function of individual in Arm i (MCS110 + chemo or chemo only) can be expressed as

$$\lambda_i(\mathrm{t}) = \lambda_0(t)e^{\beta X_i}$$

Here $\lambda_0(t)$ is the baseline hazard (or hazard for chemo arm), X_i indicates the treatment arm membership (0 for chemo and 1 for MCS110 + chemo) and β denotes the log hazard ratio (HR) between MCS110+chemo arm and the chemo arm. Furthermore baseline or chemo arm hazard function $\lambda_0(t)$ is modeled via a piece-wise exponential model. This is a semi-parametric model

which subdivides time into reasonably small K intervals and assumes that the baseline hazard is constant in each interval. i.e.,

$$\lambda_0(t) = \lambda_{ck} \quad t \in (I_{k-1}, I_k] \text{ for } \quad k = 1,2,.....,K$$

Note that the λ_{Ck} refers to hazard for unit time (per day). Sampling model (or likelihood) under this framework can be constructed using Poisson distribution. In this model for each of the K time intervals, the number of events in the chemo arm (r_{Ck}) and MCS110+chemo arm (r_{Tk}) follow Poisson distributions with interval-specific hazards λ_{Ck}. Under the proportional hazards assumption it follows that

Chemo data: $r_{Ck} \sim \sim \text{Poisson}(e_{Ck}\,\lambda_{Ck})$,

MCS110+chemo data: $r_{Tk} \sim \text{Poisson}(e_{Tk}\,e^{\beta}\,\lambda_{Ck})$,

where e_{Ck} and e_{Tk} are risk sets for event in the chemo and MCS110+chemo arm, respectively, in interval $(I_{k-1}, I_k]$ and L_k is the length of the k-th interval.

The study plans to enroll approximately 78 patients to accrue 58 events for the primary analysis of PFS endpoint. This study will be considered successful if there is sufficient evidence that the combination of MCS110 with chemotherapy is superior to chemotherapy only in PFS based on the evaluation criteria, i.e.:

- Posterior probability (HR >1) < 10%, and
- Posterior median HR ≤ 0.7.

5.6.1.2 Prior distribution

The Bayesian approach requires the specification of prior distributions for the model parameters. In this section we illustrate the specification of weakly informative prior for interval specific hazards (λ_k's) using relevant data for chemo arm from publications and non-informative prior for log hazard ratio (β).

5.6.1.2.1 Prior for Log Hazard Ratio (β)

The prior distribution for the log hazard ratio β was assumed non-informative, $\beta \sim N(\text{mean}=0, \text{sd}=10)$.

5.6.1.2.2 Prior Derivation for Interval Specific Hazard (λ_k's)

A weakly informative prior for $\log(\lambda_{Ck})$ as N(mean = -1.892569, sd = 5) will be used for interval specific hazards (λ_k's) to reflect the historical hazard rate for the chemo arm but allowing for considerable prior uncertainty to handle possible prior-data conflict to the chemo arm in the current trial.

5.6.2 Operating Characteristics

The purpose of this section is to present the operating characteristics of the proposed design under various scenarios. The data for the chemo arm are simulated such that for some scenarios they are in alignment with the historical control data and for the others, they are not. Different

magnitudes of efficacy are also considered, e.g, no efficacy, moderate efficacy and substantial efficacy under different scenarios. Type I error rate and power for this design under different scenarios will be investigated as mentioned in detail in the next section.

5.6.2.1 Scenarios investigated

In order to investigate the operating characteristics, data are simulated under the scenarios as described in Table 5-3.

Table 5-3 Different Scenarios of Operating Characteristics simulations

Scenario#	Current control aligned with prior?	Efficacy Magnitude	Median PFS, chemo arm (months)	Median PFS, MCS110+chemo arm (months)	True Hazard Ratio
1	Yes	No efficacy	4.6	4.6	1
2	Yes	Substantial	4.6	9.2	0.5
3	Yes	Moderate	4.6	6.6	0.7
4	No	No efficacy	6	6	1
5	No	Substantial	6	12	0.5
6	No	Moderate	6	8.6	0.7

As shown in the Table 5-3, chemo data are simulated to be aligned with the prior for scenarios 1-3. Different magnitudes of efficacy will be tested in these three scenarios by varying the true hazard ratio. For scenario 1, hazard ratio 1 means that there is no efficacy. The simulation output in this case provides Type I error rate. For the other two scenarios, powers are obtained. Similarly for scenarios 4-6, chemo data not aligned with prior are simulated and scenario 4 is the case with no efficacy where the simulation result provides Type I error rate.

5.6.2.2 Simulation study description

Each of the above described scenarios is investigated based on simulated data over 1000 trials. The following assumptions are made in order to run these simulations:

1. The time to event (PD or death), censoring time and accrual time are all assumed to follow exponential distribution. For all the above scenarios the accrual is assumed to be 6 patients per month.
2. The End of Study is assumed to be on the day of the 58th event.

Simulation is performed in the following steps:

Step 1:

Based on the assumed distributions of time to event and accrual time, PFS data are simulated for patients in the MCS110+chemo arm and chemo arm (randomization ratio 2:1) sequentially until the required number of events (58 events) is reached.

Step 2:

The simulated data is then transformed as the number of patients at risk and number of events in different time intervals for each treatment arm similar to historical data. But the total number of interval in the simulation depends on maximum event/censored time.

Step 3:

As mathematical closed form are not tractable, hence, posterior distributions for the log(HR) from Bayesian Cox PH model are computed via MCMC combining the weakly informative prior with the simulated transformed data.

Step 4:

Claim positive result for the Bayesian method if {Posterior median HR $\leq$ 0.7 and posterior Prob(HR>1) $<$ 0.1}.

Step 5:

Repeat step 1-4 for 1000 trials. Calculate the rate of positive results.

5.6.2.3 Simulation study results

Table 5-4 shows the operating characteristics for the six scenarios.

Table 5-4 Operating characteristics for the six scenarios

Scenario	Median PFS chemo arm (months)	Median PFS MCS110+chemo arm (months)	HR	Type I error/ Power	Estimated HR
1	4.6	4.6	1	0.089	1.056
2	4.6	9.2	0.5	0.878	0.531
3	4.6	6.6	0.7	0.465	0.742
4	6	6	1	0.088	1.051
5	6	12	0.5	0.886	0.522
6	6	8.6	0.7	0.497	0.736

Results from Table 5-4 show that the Bayesian Cox PH model using weakly informative prior yields reasonable 1-sided type I error (0.088-0.089) and power (0.465-0.886) under different scenarios in alignment between current and historical data.

5.7 Rule of exclusion criteria of analysis sets

The rules for subject classification in the analysis sets (FAS, Safety, PPS, and PAS) based on protocol deviation specifications (Table 5-5) and non-protocol deviation classification criteria (Table 5-6), are described below.

Table 5-5 Protocol deviations that cause subjects to be excluded

Deviation ID	Description of Deviation	Exclusion from Analysis Set
INCL02	Patient must have histological or cytological evidence of estrogen-receptor negative (ER-), progesterone receptor negative (PgR-) and human epidermal growth factor-2 receptor negative	PPS

Deviation ID	Description of Deviation	Exclusion from Analysis Set
	(HER2-) BC by local laboratory testing, based on last available tumor tissue.	
INCL03	Patient must provide a pre-treatment tumor biopsy demonstrating high TAM content as assessed per the central laboratory (approximately 15% of TAMs or above) (under PA1)	PPS
INCL05	Patient must have at least one measurable lesion per RECIST 1.1 (including lytic or mixed bone lesions with an identifiable soft tissue component that meets the measurability criteria) **or** non-measurable bone lesions in the absence of measurable disease.	PPS
INCL09	Patient must provide a pre-treatment tumor biopsy demonstrating high TAM content as assessed per the central laboratory (under PA 2)	PPS
EXCL07	Patient must not receive concomitant immunosuppressive agents or chronic corticosteroids (≥10 mg of prednisone or equivalent) at the time of first dose of study drug.	PPS
EXCL18	Patient must not participate in parallel investigational drug or device studies.	PPS
EXCL24	Patient must not have had a prior chemotherapy (given for ≥ 21 days) for advanced BC- and patients must not have had a prior chemotherapy with carboplatin, cisplatin or gemcitabine in the adjuvant or neoadjuvant setting if less then 12 months have passed since the last administration (under PA 2)	PPS
COMD01	Patient received another anticancer or investigational treatment while on study treatment.	PPS
COMD02	Patient received concomitant chronic corticosteroids (≥10 mg of prednisone or equivalent) while on study.	PPS
COMD03	Patient received other biologics ((eg: antibodies and proteins) or immunosuppressive medication while on study.	PPS
TRT01	Misrandomization: Patient received investigational treatment which was different from the one assigned by the randomization system	PPS
OTH03	Method used to evaluate lesions has changed from baseline method	PPS
OTH05	Patient with no PK sample collected	PAS

Table 5-6 Subject Classification

Non-PD criteria that cause subjects to be excluded	Exclusion from Analysis Set
No informed consent	FAS
Not randomized	
No informed consent	Safety Set
Not randomized	

Non-PD criteria that cause subjects to be excluded	Exclusion from Analysis Set
No study treatment taken	
No valid post-baseline safety assessment	
Not in FAS	PPS
No adequate tumor assessment at baseline	
No follow-up tumor assessment ≥6 weeks after starting treatment nor PD < 6 weeks	
No evaluable PK data	PAS

6 Reference

O'Shaughnessy J, Osborne C, Pippen J (2011) Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer. N Engl J Med 364:205-14

NOVARTIS

Clinical Development

MCS110

CMCS110Z2201 / NCT02435680

A randomized phase II study of MCS110 combined with carboplatin and gemcitabine in advanced Triple Negative Breast Cancer (TNBC)

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
20-March-2020	Prior to final DB lock	Creation of final version	N/A – First version	NA

Table of contents

List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
BDM	Biometrics and Data Management
CR	Complete response
CRO	Contract Research Organization
CSF-1	Colony stimulation factor – 1, also called M-CSF
CSP	Clinical study protocol
CSR	Clinical study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTX-I	C-terminal telopeptide of type I collagen, a bone reabsorption marker
DAR	Dose administration record
DBL	Database lock
DI	Dose intensity
DMC	Data Monitoring Committee
DOR	Duration of response
DRI	Drug reference listing
ECG	Electrocardiogram
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
HR	Hazard ratio
IHC	Immunohistochemistry
INR	International normalized ratio
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantificaton
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall respolnse rate
OS	Overall Survival
PD	Pharmacodynamics
PDI	Planned dose intensity
PDS	Programming Datasets Specifications
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PR	Partial response
PRO	Patient-reported Outcomes
QoL	Quality of Life
RAP	Report and Analysis Process

RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International System of Units
SOC	System Organ Class
SSD	Study specification document
TAM	Tumor-associated macrophages
TFLs	Tables, Figures, Listings
TIL	Tumor-infiltrating lymphocytes
TNBC	Triple Negative Breast Cancer
ULN	Upper Limit of Normal
WHO	World Health Organization

Introduction

This Statistical Analysis Plan (SAP) provides detailed statistical methodology for the analysis of data from study CMCS110Z2201 that will be presented in the final Clinical Study Report (CSR). The output shells (in-text and post-text) accompanying this document can be found in the Tables, Figures and Listings (TFL) shells document. The specifications for derived variable and datasets can be found in the Programming Datasets Specifications (PDS) document. This version of the SAP is based on the Protocol Amendment 6. The final CSR will be written after the final database lock.

The statistical analyses which are covered in the SAP for the primary CSR are not repeated within this document. Refer to the folloing documents stored in CREDI.

/CREDI Projects/M/MCS110Z/CREDI Studies/MCS110Z2201/Administrative Files (study level)/RAP or RAMP Meeting - CMCS110Z2201_SAP_CSR_1_primary_final.docx

https://webedi02.na.novartis.net:8443/webEDI02_non_SSO/drl/objectId/090095a88e6b01c2

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., PSUR/DSUR, MTD/RDE 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.

1.1 Study design

See the primary CSR SAP.

1.2 Study objectives and endpoints

See the primary CSR SAP.

2 Statistical methods

2.1 Data analysis general information

See the primary CSR SAP.

2.1.1 General definitions

See the primary CSR SAP.

2.1.1.1 Study drug and study treatment

See the primary CSR SAP.

2.1.1.2 Date of first/last administration of study treatment

See the primary CSR SAP.

2.1.1.3 Study day

See the primary CSR SAP.

2.1.1.4 On-treatment assessment/event

See the primary CSR SAP.

2.2 Analysis Set

See the primary CSR SAP.

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 following will be tabulated:

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

A listing of study completion by treatment will be produced using the FAS. Screen failures will not be included.

2.3.2 Basic demographic and background data

Demographic data including age, predominant race, ethnicity, height, weight and ECOG performance status will be listed and summarized by study arm and treatment group. In addition, child bearing potential will be listed, and age (<65, 65-<85, ≥85 years) category summarized.

2.3.3 Medical History

No analysis of medical history will be performed for the final CSR.

2.3.4 Prior antineoplastic therapy

No analysis of prior antineoplastic theray will be performed for the final CSR.

2.3.5 Diagnosis and extent of cancer

No analysis of diagnosis of the extent of cancer will be performed for the final CSR.

2.3.6 Protocol deviations

No analysis of protocol deviation will be performed for the final CSR.

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

The safety set will be used for all summaries and listings of study treatment.

2.4.1 Study treatment / compliance

2.4.1.1 Study treatment

See the primary CSR SAP.

The duration of exposure to each 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. 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.

2.4.1.2 Compliance

Compliance to the study treatment within each study arm/treatment group will be assessed by the number of dose reductions, number of dose interruptions and percent of cycles received planned dose for all the study drugs separately in summary tables by study arm and treatment group for the safety set.

2.4.2 Prior, concomitant and post therapies

No analysis of prior, concomitant and post therapies will be performed for the final CSR.

2.5 Analysis of the primary objective

The primary objective is to assess the anti-tumor activity of MCS110 combined with carboplatin/gemcitabine compared to carboplatin/gemcitabine in adult patients with triple negative breast cancer.

2.5.1 Primary endpoint

See the primary CSR SAP.

2.5.2 Statistical hypothesis, model, and method of analysis

See the primary CSR SAP.

For final CSR, Kaplan-Meier plots will be reproduced and summarized by treatment arm. No formal hypothesis testing will be carried out. A summary table based on Kaplan-Meier estimates of PFS by treatment arm will also be presented.

2.5.3 Handling of missing values/censoring/discontinuations

See the primary CSR SAP.

2.5.4 Supportive analyses

No supportive analysis will be performed for the final CSR.

2.6 Analysis of the key secondary objective

NA.

2.7 Analysis of secondary efficacy objective(s)

See the primary CSR SAP.

Duration of response will be summarized and presented by treatment arm using Kaplan-Meier estimates.

2.8 Safety analyses

The Safety set will be used for summaries and listings of safety.

2.8.1 Adverse events (AEs)

Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA, version 20.1 or later) and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, respectively.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. CTCAE Grade 5 (death) is not used in this study; rather, information about deaths is summarized in a separate analysis. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

AE Summaries

AE summaries will include all AEs occurring during on-treatment period. All AEs collected in the AE (e)CRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs starting during the post-treatment period will be flagged in the listings.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT)

using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event. AE with missing CTCAE grade will be included in the 'All grades' column of the summary tables.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency of "All grades" column, as reported in the "All patients" column.

The following summaries will be produced for all AEs starting or worsenining during the on-treatment periods by treatment: AEs by SOC and/or PT, summarized by severity, relationship, seriousness and leading to treatment discontinuation

EudraCT and clinicaltrials.gov requirements for AEs and Deaths summaries

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on-treatment adverse events which are not serious adverse events with an incidence greater than 5% and on-treatment SAEs and SAEs suspected to be related to study treatment will be provided by SOC and PT on the safety set population.

If for a same Subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

Separate summaries for on-treatment and all deaths (including post-treatment death) will be produced by treatment, system organ class and preferred term.

All deaths will be listed for the safety set, post treatment deaths will be flagged.

2.8.3 Laboratory data

No analysis of laboratory data will be performed for the final CSR.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

No ECG and cardiac imaging data will be analyzed for the final CSR.

2.8.4.2 Vital signs

No vital signs data will be analyzed for the final CSR.

2.9 Pharmacokinetic analysis

No pharmacokinetic data will be analyzed for the final CSR.

2.10 Biomarkers

See the primary CSR SAP.

Tables with descriptive statistics summarizing the TAM and TIL content, circulating CSF-1 level and serum CTX-1 level, at baseline and post-baseline will be provided. Data will be listed by patient for TAM and TIL content, as well as circulating CSF-1 level and serum CTX-1 level. Safety set will be used for all summaries and listings.

2.11 Exploratory analyses

No exploratory analyses will be executed for the final CSR.

2.12 Interim analysis

See the primary CSR SAP.

3 Sample size calculation

See the primary CSR SAP.

4 Change to protocol specified analyses – CSR Section 9.8.3

For the final CSR, only limited demographic, disposition, exposure, efficacy, biomarker and safety data will be analysed.

5 Appendix

5.1 Baseline

Baseline is the last available and valid assessment performed or value measured within 28 days 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, samples for biomarkers).

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.

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

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

5.2 Handling of missing and partial dates

For patients not known to have died prior to the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will be reported as continuing at the cut-off date. For these events, the end date will not be imputed.

For patients known to have died prior to or on the cut-off date:

All events (e.g. AEs and concomitant medications) that started before or on the cut-off date, and with end date missing or after the cut-off date will have the end date imputed to the date of death. For these events, the imputed end date will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. a dose administration record with missing end date, or last date of study treatment is after the cut-off date), the end date will be imputed to the cut-off date in order to calculate e.g., the duration of exposure to study treatment. The imputed date will be displayed and flagged in the listings.

5.3 Construction of waterfall graphs

Waterfall graphs will be used to depict anti-tumor activity. These plots will display the best percentage change from baseline in the sum of diameters of target lesions for each patient.

Note: Patients without any valid assessments to calculate a percentage change from baseline value will be excluded from the graphs. Assessments with an unknown overall response will be included as long as the sum of diameters of target lesions is correctly computed on the same lesions assessed at baseline.

Patients will be ordered in the graph from left (worst change) to right (best change).

1. Bars above the horizontal axis (0%) representing tumor growth,

2. Bars under the horizontal axis (0%) representing tumor shrinkage.

A special symbol (e.g. $*$) will be added below the bottom of respective bars for confirmed RECIST response (CR or PR), with corresponding specificatons in footnote. The total number of patients displayed in the graph (n) over the total number of patients in the FAS (N) will be shown. The best overall response (BOR) will be shown above each of the displayed bars in the graph. Symbols will be used to differentiate groups of interest, i.e. study arm. A horizontal threshold line at -30% will be shown.

5.4 Imputation rules

5.4.1 Study drug

Dose administration record with missing or partial dates are not acceptable, and should always be queried. The start and end dates for each DAR are expected to be the same.

5.4.2 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	01MONYYYY
(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.

5.4.3 Medication/therapy date imputation

5.4.3.1 Prior antineoplastic therapy date imputation

The imputation of a prior therapy start date will follow the same conventions as for an AE start date (see Section 5.4.2 AE date imputation), with the exception that scenario (B) will be replaced to be 'Start date of study treatment – 1'.

For missing end date imputation:

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

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

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

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

5.4.3.2 Concomitant medication date imputation

The imputation of a concomitant medication start date will follow the same conventions as for an AE start date (see Section 5.4.2 AE date imputation). No imputation will be performed for concomitant medication end dates.

5.4.3.3 Post antineoplastic therapy date imputation

Post therapies date imputation should not have to be considered. Any data entered in the eCRF pages are considered as starting after the last treatment, after being queried and verified.

5.5 Laboratory parameters derivations

Serum creatinine clearance is derived according to the Cockcroft-Gault equation: (140-age (years)) × weight (kg) (× 1.04 if female) / (serum creatinine (umol/L)).

Corrected Calcium (mg/dL) = 0.8 × (Normal Albumin (g/dL) – Albumin (g/dL)) + Serum Calcium (mg/dL), where normal albumin is 4 g/dL.

5.6 Statistical models

5.6.1 Primary analysis

In the following, the statistical model and prior distributions for the Bayesian Cox proportional hazard (PH) model will be described. We consider here the use of historical data of the same patient population to enrich the chemo arm (Arm 2).

5.6.1.1 Model Specification

The primary analysis of progression free survival (PFS) will be based on a Bayesian Cox PH model. This model will be used to estimate the hazard ratio for PFS of Arm 1 vs. Arm 2. This model assumes that the hazard function of individual in Arm i (MCS110 + chemo or chemo only) can be expressed as

$$\lambda_i(\mathrm{t}) = \lambda_0(t)e^{\beta X_i}$$

Here $\lambda_0(t)$ is the baseline hazard (or hazard for chemo arm), X_i indicates the treatment arm membership (0 for chemo and 1 for MCS110 + chemo) and β denotes the log hazard ratio (HR) between MCS110+chemo arm and the chemo arm. Furthermore baseline or chemo arm hazard function $\lambda_0(t)$ is modeled via a piece-wise exponential model. This is a semi-parametric model which subdivides time into reasonably small K intervals and assumes that the baseline hazard is constant in each interval. i.e.,

$$\lambda_0(t) = \lambda_{ck} \quad t \in (I_{k-1}, I_k] \quad \text{for} \quad k = 1,2,\ldots..,K$$

Note that the λ_{Ck} refers to hazard for unit time (per day). Sampling model (or likelihood) under this framework can be constructed using Poisson distribution. In this model for each of the K time intervals, the number of events in the chemo arm (r_{Ck}) and MCS110+chemo arm (r_{Tk}) follow Poisson distributions with interval-specific hazards λ_{Ck}. Under the proportional hazards assumption it follows that

Chemo data: $r_{Ck} \sim \sim \text{Poisson}(e_{Ck}\,\lambda_{Ck})$,

MCS110+chemo data: $r_{Tk} \sim \text{Poisson}(e_{Tk}\,e^{\beta}\,\lambda_{Ck})$,

where e_{Ck} and e_{Tk} are risk sets for event in the chemo and MCS110+chemo arm, respectively, in interval $(I_{k-1}, I_k]$ and L_k is the length of the k-th interval.

The study plans to enroll approximately 78 patients to accrue 58 events for the primary analysis of PFS endpoint. This study will be considered successful if there is sufficient evidence that the combination of MCS110 with chemotherapy is superior to chemotherapy only in PFS based on the evaluation criteria, i.e.:

- Posterior probability (HR >1) < 10%, and
- Posterior median HR ≤ 0.7.

5.6.1.2 Prior distribution

The Bayesian approach requires the specification of prior distributions for the model parameters. In this section we illustrate the specification of weakly informative prior for interval specific hazards (λ_k's) using relevant data for chemo arm from publications and non-informative prior for log hazard ratio (β).

5.6.1.2.1 Prior for Log Hazard Ratio (β)

The prior distribution for the log hazard ratio β was assumed non-informative, $\beta \sim N(\text{mean}=0, \text{sd}=10)$.

5.6.1.2.2 Prior Derivation for Interval Specific Hazard (λ_k's)

A weakly informative prior for $\log(\lambda_{Ck})$ as N(mean = -1.892569, sd = 5) will be used for interval specific hazards (λ_k's) to reflect the historical hazard rate for the chemo arm but allowing for considerable prior uncertainty to handle possible prior-data conflict to the chemo arm in the current trial.

5.6.2 Operating Characteristics

The purpose of this section is to present the operating characteristics of the proposed design under various scenarios. The data for the chemo arm are simulated such that for some scenarios they are in alignment with the historical control data and for the others, they are not. Different magnitudes of efficacy are also considered, e.g, no efficacy, moderate efficacy and substantial efficacy under different scenarios. Type I error rate and power for this design under different scenarios will be investigated as mentioned in detail in the next section.

5.6.2.1 Scenarios investigated

In order to investigate the operating characteristics, data are simulated under the scenarios as described in Table 5-3.

Table 5-3 Different Scenarios of Operating Characteristics simulations

Scenario#	Current control aligned with prior?	Efficacy Magnitude	Median PFS, chemo arm (months)	Median PFS, MCS110+chemo arm (months)	True Hazard Ratio
1	Yes	No efficacy	4.6	4.6	1
2	Yes	Substantial	4.6	9.2	0.5
3	Yes	Moderate	4.6	6.6	0.7
4	No	No efficacy	6	6	1
5	No	Substantial	6	12	0.5
6	No	Moderate	6	8.6	0.7

As shown in the Table 5-3, chemo data are simulated to be aligned with the prior for scenarios 1-3. Different magnitudes of efficacy will be tested in these three scenarios by varying the true hazard ratio. For scenario 1, hazard ratio 1 means that there is no efficacy. The simulation output in this case provides Type I error rate. For the other two scenarios, powers are obtained. Similarly for scenarios 4-6, chemo data not aligned with prior are simulated and scenario 4 is the case with no efficacy where the simulation result provides Type I error rate.

5.6.2.2 Simulation study description

Each of the above described scenarios is investigated based on simulated data over 1000 trials. The following assumptions are made in order to run these simulations:

1. The time to event (PD or death), censoring time and accrual time are all assumed to follow exponential distribution. For all the above scenarios the accrual is assumed to be 6 patients per month.
2. The End of Study is assumed to be on the day of the 58th event.

Simulation is performed in the following steps:

Step 1:

Based on the assumed distributions of time to event and accrual time, PFS data are simulated for patients in the MCS110+chemo arm and chemo arm (randomization ratio 2:1) sequentially until the required number of events (58 events) is reached.

Step 2:

The simulated data is then transformed as the number of patients at risk and number of events in different time intervals for each treatment arm similar to historical data. But the total number of interval in the simulation depends on maximum event/censored time.

Step 3:

As mathematical closed form are not tractable, hence, posterior distributions for the log(HR) from Bayesian Cox PH model are computed via MCMC combining the weakly informative prior with the simulated transformed data.

Step 4:

Claim positive result for the Bayesian method if {Posterior median HR ≤ 0.7 and posterior Prob(HR>1) < 0.1}.

Step 5:

Repeat step 1-4 for 1000 trials. Calculate the rate of positive results.

5.6.2.3 Simulation study results

Table 5-4 shows the operating characteristics for the six scenarios.

Table 5-4 Operating characteristics for the six scenarios

Scenario	Median PFS chemo arm (months)	Median PFS MCS110+chemo arm (months)	HR	Type I error/ Power	Estimated HR
1	4.6	4.6	1	0.089	1.056
2	4.6	9.2	0.5	0.878	0.531
3	4.6	6.6	0.7	0.465	0.742
4	6	6	1	0.088	1.051
5	6	12	0.5	0.886	0.522
6	6	8.6	0.7	0.497	0.736

Results from Table 5-4 show that the Bayesian Cox PH model using weakly informative prior yields reasonable 1-sided type I error (0.088-0.089) and power (0.465-0.886) under different scenarios in alignment between current and historical data.

6 Reference

O'Shaughnessy J, Osborne C, Pippen J (2011) Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer. N Engl J Med 364:205-14