NOVARTIS

Clinical Development

MCS110

Oncology Clinical Protocol CMCS110Z2201 / NCT02435680

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

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List of abbreviations

Advanced BC	Advanced breast cancer
[redacted]	[redacted]
AE	Adverse Event
ALK	Anaplastic lymphoma kinase
ALAT	Aspartate aminotranferase
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ASAT	Aspartate transaminase
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve of plasma/serum drug concentration versus time curves
b.i.d.	*bis in diem*/twice a day
carbo	Carboplatin
CDP	Clinical Development Plan
CK	Creatinine kinase
CL	Clearance
Cmax	Peak plasma/serum drug concentration after administration
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSF-1	Colony stimulation factor -1 also called M-CSF
CSF-1R	Colony stimulation factor -1 receptor
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CTX-1	C-terminal telopeptide of type I collagen, a bone reabsorption marker
DBL	Database lock
DDI	Drug-drug interaction
dFdU	2',2'-difluoro-deoxyuridine, the primary metabolite of gemcitabine
DLT	Dose Limiting Toxicity
DOR	Duration of response
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
ER	Estrogen receptor
FAS	Full Analysis Set
FU	Follow-up
gem	Gemcitabine
GGT	Gamma-glutamyl transpeptidase
GM-CSF	Granulocyte macrophage colony stimulating factor
iv	intravenous(ly)
HA	Health Authority
HER-2	Human Epidermal Growth Factor Receptor -2
HR	Hazard ratio
HV	Healthy volunteer
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee

IM	Immunomodulatory
IRB	Institutional Review Board
LAR	Luminal androgen receptor
LLOQ	Lower limit of quantitation
LMWH	Low molecular weight heparin
mAB	Monoclonal Antibody
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
M-CSF	Macrophage colony stimulating factor also called CSF-1
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
o.d.	*omnia die*/once a day
OR	Overall Response
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PET	Positron emission tomography
PFS	Progression Free Survival
PgR	Progesterone receptor
PK	Pharmacokinetics
p.o.	*per os*/by mouth/orally
PHI	Protected Health Information
PPS	Per-Protocol Set
PR	Partial response
PVNS	Pigmented Villonodular Synovitis
QW	Once-weekly
Q3W	Once every three weeks
Q4W	Once every four weeks
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
SAE	Serious Adverse Event
SD	Stable disease
TAM	Tumor associated macrophage
TIL	Tumor infiltrating lymphocyte
TIO	Tumor induced osteolysis
TNBC	Triple negative breast cancer
TRAP	Tartrate-resistant acid phosphatase
ULOQ	Upper Limit Of Quantification
w/wo	with/without

Glossary of terms

Assessment	A procedure used to generate data required by the study
Adjuvant	Treatment that is given in addition to the primary treatment (surgery). Curative intent.
Advanced breast cancer	Metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g.: q28 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Neoadjuvant	Therapeutic agents that are given before the main treatment (often surgery). Curative intent.
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject/healthy volunteer who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later

Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Supportive treatment	Refers to any treatment required by the exposure to a study treatment, e.g. premedication of vitamin supplementation and corticosteroid for pemetrexed disodium.
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Amendment 6 (11-Oct-2017)

Amendment rationale

Novartis has halted the recruitment to study MCS110Z2201 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 purpose of this amendment is to reduce the schedule of assessments while still ensuring adequate safety monitoring in order to reduce the burden to patients who remain on study treatment.

As a result of the enrollment halt, the primary objective, to assess the anti-tumor activity of MCS110 combined with carboplatin and gemcitabine (carbo/gem), will not be reached. Therefore, the frequency of RECIST assessments will be changed from every 9 weeks to a minimum of every 12 weeks. Central review of the radiological images will not be performed. Survival and Disease Progression Follow-Up will be removed from the protocol. In addition, the timing of writing the CSR will be changed, as the original timing of 58 Progression Free Survival (PFS) events will not be reached due to the recruitment halt.

In addition, all biomarker sample collections will be removed as the secondary [redacted] endpoints will not be reached.

Since the pharmacokinetics (PK) of MCS110 is now well characterized, PK and CSF-1 samples will no longer be collected. [redacted] Sufficient PK samples have been collected to confirm the PK of carbo/gem and to draw preliminary conclusions on Drug Drug Interaction between MCS110 and carbo or gem. Therefore, the PK samples for carbo/gem will no longer be collected.

Other minor changes were made for consistency and/or clarifications.

Study update

The amended protocol version 05 has been submitted to HAs and IRB/IECs. Last patient first treatment (LPFT) occurred on July 17th, 2017. In total, 49 patients have been treated on study. Eight patients are still under treatment and 41 patients have been discontinued from the study.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Section 1.4.2 Clinical

- Section updated with new safety information

Table 3-1 Objectives and related endpoints

- Overall Survival has been removed from the secondary objectives

Section 4.1 Description of study design Fig 4-2 Study visit flow

- Survival FU and Disease progression FU have been removed from the study design

Section 4.2 Definition of end of the study:

- Survival follow-up has been removed

Table 7-1: Visit Evaluation Schedule:

- Survival FU and Disease Progression FU have been removed
- CA 15-3 sample collections have been removed
- Biomarker sample collections have been removed
- Tumor evaluation has been updated to specify that tumor evaluations will be performed with a minimum of every 12 weeks
- Central ECG evaluation at C8D1 has been replaced by a local evaluation
- PK sample collection for MCS110 and carbo/gem, CSF-1 sample collection [redacted] have been removed

Section 7.1.4 Discontinuation of study treatment

- Section has been updated to remove Disease progression FU

Section 7.1.6 Follow-Up period

- Section has been updated to remove Disease Progression FU and Survival FU

Section 7.2.1 Efficacy assessments

- Section has been updated to specify that tumor assessments will be performed with a minimum of every 12 weeks
- Section has been updated to remove the central review of the radiological imaging

Section 7.2.2.5.3 Tumor markers

- Section has been updated to specify that following local IRB/EC approval of protocol amendment 6, tumor markers sample collection will no longer be required by the protocol.

Section 7.2.2.6.1 Electrocardiogram

- Section has been updated to specify that the ECG at C8D1 will be reviewed locally instead of centrally

Section 7.2.3.1 Blood sample collection

- Section updated to specify that following local IRB/EC approval of protocol amendment 6, PK sample collection for MCS110 and carbo/gem will no longer be required. In addition, CSF-1 [redacted] sample collection will no longer be required.

PK tables 7-6, 7-7 and 7-8

- PK tables updated to specify that PK samples will no longer be collected after approval of protocol amendment 6

Section 7.2.4 Biomarkers

- Section updated to specify that following local IRB/EC approval of protocol amendment 6, biomarker sample collections will no longer be required by the protocol.

Table 7-9 Biomarker sample collection plan

- Table updated to specify that biomarker samples will no longer be collected after approval of protocol amendment 6.

Section 9.3 Data Collection and section 9.4 Database management and quality control

- Sections have been update to specify that the ECG's will be reviewed centrally only until cycle 4

Section 10 Statistical method and data analysis

- Section has been updated regarding the timing of the clinical study report

Section 10.5.1 Other secondary efficacy objectives

- Section has been updated to remove the overall survival

Section 11.5 Publication of study protocol and results

- Section updated to reflect the most recent publication policy from Novartis

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent Form for the patients. Sites are required to update and submit for approval a revised Informed Consent Form that takes into account the changes described in this protocol amendment.

Summary of previous amendments

Amendment 5 (04-May-2017)

Amendment rationale

The purpose of this amendment is to address requested changes from a Health Authority (HA) regarding the post-treatment contraception period for carboplatin and gemcitabine.

The minimum required post-treatment contraception period is 30 days per protocol amendment 4. However, local variations regarding the required post-treatment contraception period have been detected in the participating countries' approved labels for the chemotherapy. Therefore, the post-treatment contraception period for carboplatin and gemcitabine will be updated to follow the local approved labels with a minimum follow-up of 30 days. Furthermore, monthly urine pregnancy tests must be performed during the post-treatment contraception period according to local approved label.

In addition, a minor clarification has been made about the radiological assessments following another HA request.

Furthermore, a minor correction was made to the ECG footnote reference in the visit evaluation schedule (Table 7-1).

Study Updates

The amended protocol version 04 has been submitted to HAs and IRB/IECs. As of April 19th, 2017, 33 patients have received study treatment.

Changes to protocol

Section 5.3: Exclusion criterion number 14:

- Exclusion criterion 14 updated as follows: "Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 90 days after the last dose of MCS110, or for 30 days after the last dose of carboplatin and gemcitabine or as recommended per the local approved labels for carboplatin and gemcitabine, whichever has the longest duration".

Table 7-1: Visit evaluation schedule:

- Footnote 4 has been updated to reflect that any pregnancy test in the safety follow-up will be reported in the source documentation and that monthly urine pregnancy tests must be performed for 90 days after the last dose of MCS110 or for 30 days after the last dose of carboplatin and gemcitabine or as recommended per the local approved labels for carboplatin and gemcitabine, whichever has the longest duration.
- Footnote 8 has been deleted as all the information about the pregnancy tests in the safety follow-up is captured in footnote 4.

Section 7.2.1 Efficacy assessments:

- Section updated to clarify that radiological assessments obtained for patients enrolled on study will be centrally collected and stored by an imaging CRO designated by Novartis for a potential centralized blinded review in addition to the local assessment if deemed necessary.

Section 7.2.2.5.6: Pregnancy

- Section updated to specify that for both arms, if the post-treatment contraception period for carboplatin and gemcitabine as per the local approved label is longer than 30 days, additional monthly urine pregnancy tests must be performed until the end of the post-treatment contraception period.

Section 8.3: Pregnancies

- Section updated to specify that any pregnancies occurring after discontinuation of study treatment (up to 90 days or during the post treatment contraception period as recommended per the local approved labels, whichever has the longest duration) must be reported to Novartis within 24 hours of learning of its occurrence.

Section 10.4.1: Variable

- Section updated to specify that if blinded central review is performed on the radiological assessments, then analyses specified for all efficacy endpoints based on local assessments will be additionally performed on the response evaluations from the blinded review.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent Form for the patients. Sites are required to update and submit for approval a revised Informed Consent Form that takes into account the changes described in this protocol amendment.

Amendment 4 (20-Sep-2016)

Amendment rationale

The main purpose of this amendment is to extend the post-treatment contraception period from 60 to 90 days for patients receiving MCS110.The post-treatment contraception period was set to 60 days based on PK data from the healthy volunteer (HV) study (CMCS110X2201) demonstrating that 99% of free MCS110 was eliminated by that time-point. Newly obtained PK data suggest that the maximum concentrations of free MCS110 are slightly higher in TNBC patients than in HV. Simulations predict that 97% of free MCS110 will be eliminated after 60 days in patients with TNBC and that after 90 days 99% of free MCS110 will be eliminated, corresponding to a free MCS110 concentration of 7 ng/mL which is below the in-vitro IC50 determined in the activity and potency assay (IC50: 10-20 ng/mL, IB edition 11 section 4.1.1.1). Thus, the post-treatment contraception period will be extended from 60 days to 90 days.

Accordingly, the safety follow-up will also be extended from 60 to 90 days. During the safety follow-up, all AE's and SAE's, regardless of causality, will be collected 30 and 90 days after discontinuation of study treatment. If a patient starts a new anticancer therapy during the safety follow-up, only AE's and SAE's suspected to be related to study treatment and associated concomitant medications will be collected from this time point.

In order to add flexibility, safety follow-ups may be performed via telephone calls.

Clarifying text has been added to the protocol emphasizing that on-treatment biopsies only should be taken if medically feasible according to the treating investigator to ensure patient's safety. Furthermore, corrections of insignificant typographical errors have been made throughout the protocol.

Study Updates

The amended protocol version 03 has been submitted to HAs and IRB/IECs. As of August 16th, 2016, 20 patients have received study treatment.

Changes to protocol

Section 4.1 Description of study design, Study Visit Flow (Fig 4-2)

Section 7 - Table 7-1 Visit Evaluation Schedule

Section 7.1.6 .Follow-Up Period

Section 7.2.2.5.6 Pregnancy

Section 8.1.1 .Adverse Events Definitions and Reporting

Section 8.2.2 .Serious Adverse Events Reporting

Section 10.5.2.1 .Analysis Set and Grouping for the Analyses

- All sections listed above updated to reflect the new safety follow-up period of 90 days

Section 5.3 Exclusion Criterion 14

- Updated to reflect the 90 days contraception period after the last dose of MCS110 and the 30 days contraception period after the last dose of carboplatin and gemcitabine for patients not receiving MCS110.

Table 7-1 Schedule of Evaluation, Section 7.1.6 Follow-Up period, Section 8.1.1 Adverse Events Definitions and Reporting and Section 8.2.2 Serious Adverse Events Reporting

- Table and Sections changed to reflect that once a patient begins another anti-cancer therapy, only AE's and SAE's suspected to be related to the study treatment and the associated medications will be collected in the follow-up period.

Section 7.1.6 Follow-up period

- Section updated to reflect the option to perform the safety follow-up via telephone call

Section 7.2.2.5.6 Pregnancy

- Updated to reflect that for women of childbearing potential during the safety follow-up period, urine pregnancy tests are performed 30, 60 and 90 days after stopping MCS110 in Arm 1 and 30 days after stopping study treatment in Arm 2.

Section 7.2.4 Table 7-9 Biomarker sample collection plan

- Table is updated to clarify that biopsies should be taken if medically feasible
- Additionally a footnote has been added that all biopsies must be conducted by a professional with expertise in the procedure

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent Form for the patients. Sites are required to update and submit for approval a revised Informed Consent Form that takes into account the changes described in this protocol amendment.

Amendment 3 (08-Apr-2016)

Amendment rationale

The main purpose of this amendment is to provide additional flexibility for MCS110 dosing by introducing the option to skip the additional MCS110 dose on C1D8 for subsequent patients, should any safety concerns be revealed upon review of data from the dosing regimen currently being evaluated.

The current study design includes an early safety review meeting, which will be performed after the first 9 patients have been randomized and completed 2 treatment cycles of either MCS110 + carboplatin/gemcitabine or carboplatin/gemcitabine alone, or discontinued earlier due to an adverse event. Novartis and study investigators will evaluate clinical, PK and laboratory data at a joint meeting to make an assessment of the safety of both study arms. If safety concerns are noted, the only current option is to reduce the MCS110 dose to 5 mg/kg and to keep the additional 5 mg/kg dose of MCS110 on Cycle 1 Day 8. This amendment introduces the option to skip the additional MCS110 dose on C1D8 for subsequent patients. If the dosing regimen is changed after the data review, an additional safety review will take place after 9 patients have been randomized and completed 2 cycles of either MCS110 (per the new dosing regimen) + carboplatin/gemcitabine or carboplatin/gemcitabine alone. Any subsequent changes of the MCS110 dosing regimen will be followed by an additional safety review per the procedure just described. The lowest accepted MCS110 dosing regimen will be 2.5 mg/kg, with or without the additional dose on C1D8.

Furthermore, other updates are being implemented in this protocol amendment as described below:

- The lowest possible dose reduction for MCS110 has been changed from 2.5 mg/kg to 1 mg/kg to allow dose reductions for the alternative lower MCS110 dosing regimens.
- Dose delay ≤ 1 week will be permitted for any reason. In case treatment cannot be delivered within this time frame the dose will be skipped.
- A note has been added to clarify that dose reductions for hematological toxicities suspected to be related to carbo/gem should not be performed based on nadir counts for platelets or neutrophils
- Clarification has been added that all tumor biopsies are mandatory and may only be omitted for medical or safety reasons.
- The on-treatment biopsy should be taken between C2D8 – C3D1, but may be delayed to a later time point at the investigator's discretion.

In addition, corrections of insignificant typographical errors have been made throughout the protocol.

Study Updates

The amended protocol version 02 has been submitted to HAs and IRB/IECs. As of 17-MAR-2016, 8 patients have been dosed.

Changes to protocol

Section 2.2 Rationale for study design

- Updated to reflect the new dosing alternatives for MCS110 and the potential additional safety review meetings

Section 4.1 Description of study design

- Updated to reflect the new dosing alternatives for MCS110 and the potential additional safety review meetings

Section 5.3 Exclusion criteria #14

- Updated to correct a typo: Women of child-bearing potential are allowed to participate in the trial if they are using highly effective methods of contraception during dosing of study treatment and for 60 days after the last dose of MCS110 (changed from 90 days to 60 days)

Section 6.1.1 Dosing regimen

- This section including Table 6-1 (Dose and treatment schedule) has been updated to reflect the new dosing options after the safety reviews: possibility to skip the C1D8 MCS110 dose and new treatment group added (2.5 mg/kg for MCS110).

Section 6.2.1 Dose modifications and dose delay

- Updated to reflect that the study treatment may be delayed by ≤ 1 week from the expected day of the next study treatment administration for any reason. If study treatment cannot be given within this time frame due to persisting toxicity, the dose should be skipped.
- Updated to reflect that the MCS110 dose can be reduced by 3 dose levels if the patient is in the MCS110 10 mg/kg treatment group.
- Updated lowest possible dose reduction for MCS110 from 2.5 mg/kg to 1 mg/kg.

Section 6.2.1.1 - Table 6-2 Dose modifications and actions for toxicities suspected to be related to MCS110

- A typo has been corrected: in case of Grade 3 ALT elevation the chemotherapeutic agents should be reduced by 20% and if recurring by an additional 20%, in accordance with the original publication by O'Shaughnessy 2011.

Section 6.2.1.1 - Table 6-3 Dose modifications for hematological toxicities suspected to be related to carbo/gem

- Note added to reflect that the dose reductions should not be performed based on nadir counts of neutrophils and platelets

Section 6.4.2 Treatment assignment and randomization

- Total number of patients if the dose is changed after the safety review meetings has been reevaluated to approximately 110 (including 2 additional safety cohorts of 9 patients).

Section 7 - Table 7-1 Visit Evaluation Schedule

- Pregnancy test section updated for 30 and 60 days safety follow up to reflect that the test will only be reported in source document and not in the CRF
- Footnote has been added to clarify that the MCS110 C1D8 dose may be omitted after a safety review meeting
- Phone call for survival follow-up has been moved to the survival follow-up (FU) (to correct for a typo)

Section 7.2.2.5.6 Pregnancy

- Clarification added that the pregnancy tests at 30 and 60 days safety follow-up may be a urine test instead of a serum pregnancy test and will be recorded only in the source documentation, not in the CRF.

Section 7.2.3.1 Blood sample collection and handling

- Footnote added in Table 7-6 and Table 7-7 to reflect that if the additional dose of MCS110 on C1D8 is omitted the post-dose C1D8 PK sample collection should be skipped

Section 7.2.4 Biomarkers

- Clarification has been added that all biopsies in Table 7-9 are mandatory and must be obtained if medically feasible.

Table 7-9 Biomarker sample collection plan

- Clarification has been added that if obtaining the biopsy is not medically feasible between C2D8 and C3D1, the biopsy may be collected at a later time point at the investigators discretion.

Section 8.2.2 Serious Adverse Events - Reporting

- Updated accordingly to the new serious adverse events guidance
- Updated to reflect that the SAEs have to be collected, regardless of suspected causality, until at least 60 days after the patient has stopped study treatment.

Section 8.5 Steering Committee

- Clarification has been added that 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.

Section 10 Statistical methods and data analysis

- As there may be multiple treatment groups within Arm 1, the data summarized or listed "by study arm" has been changed to "by Arm and treatment group".
- The sentence "Data from patients enrolled before the safety review treated at a dosing level different from the confirmed one will be analyzed as a separate group for all the analysis unless specified otherwise" has been deleted, as there might be multiple safety reviews and in addition this sentence is already covered by the last sentence from the

previous paragraph "data will be analyzed and/or presented separately for each study arm and treatment group.

Section 10.4 Primary objective

- Clarification added that for simplicity, throughout this section, the MCS110+carbo/gem arm will be used to refer to patients randomized to Arm 1 at the MCS110 final confirmed dose.

Section 10.5.2.1 Analysis set and grouping for the analyses

- Definitions of on-treatment period and post-treatment period updated to reflect the safety follow-up of 60 days

Section 10.7 Interim analysis

- Updated to reflect the addition of a subsequent safety review meeting if the dosing regimen is changed after a safety review meeting.
- Updated to clarify that a decision to stop the trial early (not for efficacy) may be made by the Steering Committee.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent Form for the patients. Sites are required to update and submit for approval a revised Informed Consent Form that takes into account the changes described in this protocol amendment.

Amendment 2 (8-Oct-2015)

Amendment rationale

The main purpose of this amendment is to allow safety monitoring of creatine kinase (CK) elevations per local guidelines, to modify the language on Tumor associated macrophages (TAM) content for patient selection, and to implement requested changes from Health Authorities (HA).

In previous MCS110 studies, aldolase testing has been used to rule out muscle damage in patients with CK elevations. However, the aldolase assay is no longer available in several participating countries and thus, will be replaced by recommendations to rule out muscle damage (myositis/rhabdomyolysis) according to local guidelines (Table 6-2 Dose modifications and action for toxicities suspected to be related to MCS110).The aldolase testing at time of CK elevation will only be performed if required by local guidelines.

Research conducted at Novartis established an immunohistochemical assay, CD163, for evaluating TAMs in Triple negative breast cancer (TNBC). Thereafter, an external lab was contracted for the central testing of TAMs. A correlation study was performed at the external lab to ensure that the same patient population was identified using the two different assay platforms. The TAM cutoff determined during assay validation at the external lab for identifying patients with a high TAM content (40% of TNBC) differed from the one determined at Novartis, which can be explained by well-known technical differences between assay platforms. The different cutoff values were strongly and significantly correlated and thus, both assay platforms identified the same patient population. Accordingly, to account for technical differences between platforms the previously provided cut-off has been removed and replaced by "high TAM content".

The following changes have been implemented to the protocol at the request of HA's:

- "Hypersensitivity to monoclonal antibodies" has been added as an exclusion criterion to reduce the risk of hypersensitivity reactions to MCS110. Additionally, language regarding monitoring of potential hypersensitivity reactions has been incorporated.
- Phosphate testing has been added to routine chemistry due to preclinical findings of hypophosphatemia.
- Change in exclusion criteria # 11 to increase ANC from $< 1.0 \times 10^9$/L to $< 1.5 \times 10^9$/L to align with the summary of product characteristics (SmPC) of gemcitabine for approved indications.
- Phenytoin medication will be cautioned for patients participating in the study since it has been described that concomitant carboplatin treatment may decrease the serum level of phenytoin.
- Dose modifications/actions for "*Others* Grade ≥ 3 toxicities suspected to be related to study drugs were missing and have been added (Tables 6-2, 6-3, 6-4).
- Additional language on the continuous safety review and aggregation of safety data that will be ongoing throughout the duration of the study has been added to the protocol (Section 8.5).

An additional dose reduction level (2.5 mg/kg) has been added for patients with starting doses of 10 mg/kg to align the lowest permitted MCS110 dose level for all patients. The wording was changed from "50% of original starting dose" to "50% of the previous dose" in the dose modification tables to allow for the additional dose reduction of MCS110.

Quantitation of circulating CD14+CD16+ and CD14+CD16- monocytes using flow cytometry has been removed from the protocol as it has shown high assay variability in a previous study with MCS110 and thus, is of low value as a pharmacodynamic (PD) marker.

Bone scan has been added as a baseline tumor assessment if clinically indicated, to adhere to the NCCN Guidelines 2015 (Principles of Monitoring Metastatic Disease).

The study population will be expanded to include patients who have received prior adjuvant/neoadjuvant treatment containing carboplatin, cisplatin and/or gemcitabine if they are considered not refractory to the drugs. Not refractory is defined as relapse or progression of disease occurring > 12 months after last administration of the drugs. Allowing patients that are not refractory to carboplatin, gemcitabine and/or gemcitabine to participate in the study will facilitate enrollment since carboplatin, cisplatin and/or is currently often given in the adjuvant setting.

Clarification has been made regarding the archival tumor sample. The archival tumor sample should be provided only if obtained at the time of initial diagnosis. If the tumor sample from the initial diagnosis is used as the newly obtained tumor sample (< 6 months), an additional archival tumor sample is not needed.

The time window for C1D15 "168 h post start of infusion of C1D8" PK of MCS110 was incorrectly specified as 24 hours and has been corrected to 8 hours.

The unscheduled and EOT PK samplings for carbo/gem were considered redundant and will therefore be removed.

Clarification that radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within 28 days of the first dose administered.

Instead of vague language "after the primary CSR cut-off date is reached", Specific cut-off (cycle 8) is provided to detail the ECG collection plan.

New pregnancy guidelines have been implemented.

In addition, corrections of insignificant typographical errors have been made throughout the protocol.

Study Updates

The amended protocol version 01 has been submitted to HAs and IRB/IECs. One patient has been dosed so far.

Changes to protocol

Section 2.1 Study rationale and purpose

- Removal of the following sentences: "Extensive work performed at Novartis has established an immunohistochemical assay for evaluating TAMs. A TAM content of 15% of the tumor area, or above, identified 40% of TNBC as TAM high and the rest as TAM low. In this study only patients with approximately 15% TAM content or higher, as determined by a central laboratory, will be included. The final cut-off for the TAM content level will be determined during test validation at the central laboratory".
- Addition of the following sentence: "The assessment of TAM content will be obtained through submission of samples to a Novartis designated laboratory where IHC for CD163 (marker of TAM) will be performed."

Section 5.2 Inclusion criteria

- "Approximately 15% of TAMs or above" has been removed from inclusion criterion # 2.

Section 5.3 Exclusion criteria

- Change in exclusion criterion # 1 to allow prior use of carboplatin, cisplatin or gemcitabine as adjuvant or neoadjuvant chemotherapy (if > 12 months has passed since last administration).
- Change in exclusion criterion # 2 to add "hypersensitivity to monoclonal antibodies" and to remove "prior use of carboplatin, cisplatin, gemcitabine".
- Change in exclusion criteria # 11 to increase ANC from $< 1.0 \times 10^9$/L to $< 1.5 \times 10^9$/L
- Change in exclusion criteria # 15 to implement the new contraception guidelines

Section 6.1.2.1 Ancillary treatments for MCS110

- "Monitoring for hypersensitivity reactions according to local guidelines" has been added.

Section 6.2.1 Dose modifications and dose delay

- The following sentence has been added: "The chemotherapy can be dose reduced by 2 dose levels (-20% and -40%, respectively) whereas MCS110 can be dose reduced by 2 or 1 dose levels depending on starting dose (from 10 mg/kg to 5 mg /kg to 2.5 mg/kg or from 5 mg/kg to 2.5 mg/kg)."

Section 6.2.1.1 Table 6-2: Dose modifications and action for toxicities suspected to be related to MCS110

- Mandatory aldolase testing at time of CK elevation has been removed
- Guidelines for further evaluation of patients with CK elevation and symptoms or elevated levels of creatinine, CK-MB or troponin I/T, to rule out myositis/rhabdomyolysis according to local guidelines have been added.
- Clarification was made that chemotherapy may be resumed at previous dose after recovery of CK-MB, troponin (I or T) and creatinine (combined with Grade ≥ 3 CK elevation).
- Section for Other Grade ≥ 3 toxicities has been added to the table
- "50% of original starting dose" was changed to "50% of the previous dose"

Section 6.2.1.1 Table 6-3: Dose modifications for hematological toxicities suspected to be related to carbo/gem

- Section for Other Grade ≥ 3 toxicities has been added to the table
- Non-hematological toxicities removed from the footnote to correct an error.

Section 6.2.1.1 Table 6-4: Dose modifications for non-hematological toxicities suspected to be related to carbo/gem

- Section for Other Grade ≥ 3 toxicities has been added to the table
- Footnote added: "As soon as requirements for non-hematological toxicities are Grade ≤1 or baseline, study treatment should be delivered".
- "50% of original starting dose" was changed to "50% of the previous dose

Section 6.3.2 Permitted concomitant therapy requiring caution

- Caution for increased risk of seizure with concomitant carboplatin and phenytoin has been added to this section.

Section 7.1, Study flow and visit schedule

- Sentence added: "Radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within 28 days of the first dose administered

Section 7.1, Table 7-1: Visit evaluation schedule

- Since the pregnancy test is performed during the screening period, within 3 days of the first dose, the pregnancy test at C1D1 is not necessary and a footnote has been added for clarification.
- Pregnancy test added at 30 days safety follow-up.
- Addition of a safety follow-up at 60 days after the last dose of study treatment, as well as related assessments, including a pregnancy test.

Section 7.1.6 Follow-up period:

- Addition of 60 days safety follow-up and associated assessments.

Section7.1.1 Molecular pre-screening

- "Approximately 15% of TAMs or above" has been removed from this section and replaced by high TAM content per central assessment.

Section 7.2.1 Efficacy Assessments

- Sentence added: "Radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within 28 days of the first dose administered."

Section 7.2.1, Table 7-2: Imaging collection plan

- Bone scan has been added as a baseline/screening evaluation (if clinically indicated)

Section 7.2.2.5, Table 7-4: Local laboratory parameters

- Phosphate testing has been added
- CD14+CD16+ / CD14+CD16- monocytes testing has been removed
- Change regarding the aldolase testing which will only be performed if required to rule out myositis/rhabdomyolysis per local guidelines
- Myoglobin (serum or urine) added: to be performed only if required to rule out myositis/rhabdomyolysis per local guidelines

Section 7.2.2.6.1 ECGs and Section 9.3 Data Collection

- Change made to central ECG review. The independent review of the ECG's by a central laboratory will occur up to cycle 8 included. After cycle 8, ECGs will be performed at the discretion of the investigator, recorded on a local ECG CRF page and will not be reviewed by the central laboratory. EoT ECG's are mandatory but will not be reviewed centrally.

Section 7.2.3.1, Tables 7-6 and 7-7: MCS110 PK sample collection log

- Scheduled time changed from 168 (±24 h) to 168 (±8 h) at C1D15

Section 7.2.3.1, Table 7-8: Carbo/Gem PK sample collection log

- EOT and Unscheduled time points have been removed.

Section 7.2.4, Table 7-9 Biomarker sample collection plan

- Clarification has been added that the archival tumor has to be provided only if available and should be from the initial diagnosis.
- Clarification has been added to the footnote that the archival tumor sample from the initial diagnosis is not required if the newly obtained tumor sample is from the initial diagnosis.

[redacted]

Section 8.5 Steering Committee

- The following text has been added to this section: "After the initial safety review, individual patient data will subsequently be reviewed on an ongoing basis and aggregate safety data and the primary endpoint will be monitored quarterly by the study team and discussed with investigators across the duration of the trial. The data review and analysis will be based on the available data in the clinical database (see Section 10.7) at the respective time."

Section 10.5.3.1.1 Basic Tables, Figures and Listings

- The analysis plan for circulating CD14+ monocytes and CD14+CD16+ monocytes has been removed.

Section 10.7 Interim Analysis

The following text has been added:

Efficacy and safety data will be reviewed on a regular basis as mentioned in 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 but may not be limited to:

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
   Outputs to be produced for the monitoring will be identified in the RAP.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRB/IEC

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 1 (4-Mar-2015)

Amendment rationale

The main reason for this amendment is to add more specific guidance for dose modifications for CK elevation suspected to be related to MCS110, following Health Authority feed-back.

Furthermore, a clarification has been added regarding severe periorbital edema.

Changes to the protocol

- Table 6-2 (Dose modifications and action for toxicities suspected to be related to MCS110) has been amended to provide more specific guidance in case of CK elevation and severe periorbital edema.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do not affect the Informed Consents.

Protocol summary

Protocol number	CMCS110Z2201
Title	A randomized phase II study of MCS110 combined with carboplatin and gemcitabine in advanced Triple Negative Breast Cancer (TNBC)
Brief title	Efficacy study of MCS110 given with carboplatin and gemcitabine in advanced TNBC.
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	To determine whether MCS110 antibody therapy improves the efficacy of carboplatin and gemcitabine (carbo/gem) in advanced TNBC patients
Primary Objective(s)	The primary objective is to assess the anti-tumor activity of MCS110 combined with carbo/gem compared to carbo/gem alone in adult patients with TNBC cancer.
Secondary Objectives	Characterize the safety and tolerability of MCS110 given in combination with carbo/gem. Characterize PK of MCS110 when combined with carbo/gem Characterize PK of carbo/gem in the presence and absence of MCS110. Characterize PD effect of MCS110 when combined with carbo/gem To assess the anti-tumor activity of MCS110 given in combination with carbo/gem as measured by additional efficacy measures.
Study design	This study is a phase II, open-label, randomized study of MCS110 in combination with carbo/gem (Arm 1) versus carbo/gem alone (Arm 2) in patients with advanced TNBC with one or more early safety reviews.
Population	Women with advanced TNBC whose tumors contain a high content of tumor associated macrophages (TAMs).

Inclusion criteria	• Adult women (≥ 18 years of age) with advanced TNBC.
	• Histological or cytological evidence of estrogen-receptor negative (ER-), progesterone receptor negative (PgR-) and human epidermal growth factor-2 receptor negative (HER2-) Breast Cancer by local laboratory testing, based on last available tumor tissue.
	  • ER/PgR negativity to follow local guidelines
	  • If IHC HER2 2+, a negative FISH test is required
	• A pre-treatment tumor biopsy demonstrating high TAM content as assessed per the central laboratory.
	• Patients must have:
	At least one measurable lesion per RECIST 1.1. (Note: Measurable lesions include lytic or mixed (lytic + blastic) bone lesions, with an identifiable soft tissue component that meets the measurability criteria)

Exclusion criteria	• Prior chemotherapy for advanced BC. Previous adjuvant/neoadjuvant chemotherapy is allowed. • Therapy for underlying malignancy within 2 weeks prior to start of study treatment: • Chemotherapy, biologic therapy (antibodies and biologically targeted small molecules) • Radiotherapy • Major surgery • Patients receiving concomitant immunosuppressive agents or chronic corticosteroids (≥10 mg of prednisone or equivalent) at the time of first study dose. • Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening. • Known history of human immunodeficiency virus or active infection with hepatitis virus or any uncontrolled active systemic infection. • Patients with the following laboratory values during screening and on Day 1 pre-dose: • Absolute Neutrophil Count (ANC) < $1.5x10^9$/L • Hemoglobin <9 g/dL • Platelets < $100x10^9$/L • Serum creatinine > 1.5 x ULN • Serum total bilirubin > 1.5 x ULN • AST/SGOT and ALT/SGPT > 3.0 x ULN
Investigational and reference therapy	MCS110, carboplatin and gemcitabine
Efficacy assessments	Tumor assessment per RECIST v.1.1
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs.
Other assessments	MCS110 and carbo/gem pharmacokinetic assessments. Pharmacodynamic markers in blood and tumor
Data analysis	The primary efficacy endpoint is progression free survival (PFS) based on local Investigator assessment, as defined in RECIST 1.1. The hazard ratio (HR) for PFS between the MCS110+ carbo/gem arm and the carbo/gem arm will be estimated. One or more early safety reviews will be performed to provide guidance on continued safe MCS110 dosing after assessment of PK, clinical and laboratory data.
Key words	MCS110; carboplatin; gemcitabine; TNBC; TAMs

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

Breast cancer is the most common cancer among women worldwide, with an estimated 1.38 million new cases in 2008, and it is also the most common cause of cancer death in women, with 458,000 deaths (Ferlay GLOBOCAN 2008). Triple-negative breast cancer (TNBC) accounts for approximately 15% of newly diagnosed breast cancers, but due to its aggressive nature a disproportionate number (25%) of TNBC are reported in the metastatic setting (Carey 2006, Dahlberg 2009).

TNBC is characterized by lack of expression of the estrogen (ER) and progesterone (PR) receptors and lack of overexpression of the human epidermal growth factor receptor 2 (HER2). The clinical course of TNBC is associated with a high probability of distant metastases, especially to the lung and brain (Dent 2007). Currently, there are no targeted therapies for this breast cancer subtype and the only treatment option is chemotherapy. Even though several studies suggest that TNBC is a highly chemosensitive disease, prognosis still remains poor with a shorter disease free interval after initial therapy and a more aggressive clinical course in the metastatic setting (Carey 2007, Liedtke 2008, Foulkes 2010). Most patients receive anthracyclines and taxanes in the adjuvant setting and no further standard of care therapy exists for patients with metastatic TNBC (NCCN 2014, ESMO guidelines 2014). However, emerging data suggest that platinum salts (ie, cisplatin and carboplatin) are highly active in early and advanced TNBC, and therefore widely used in the clinical setting (O'Shaughnessy 2011, von Minckwitz 2014). Median survival for metastatic TNBC is approximately 1 year, making TNBC a disease with high unmet medical need (Kassam 2009).

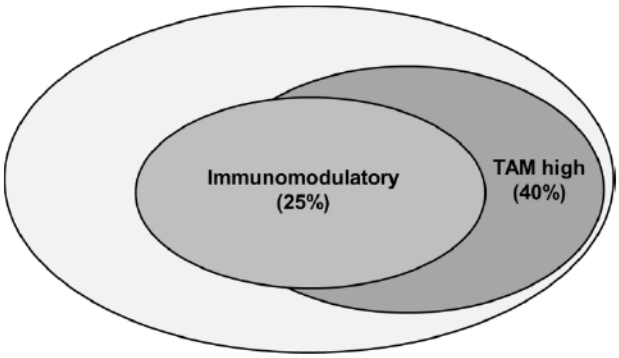
1.1.1 The immunomodulatory (IM) subtype of TNBC

Recently 6 different subtypes of TNBC were described using gene expression profiling: two basal-like, one mesenchymal, one mesenchymal stem-like, one luminal androgen receptor (LAR) and one immunomodulatory (IM) subtype (Lehmann 2011). Ongoing and emerging treatment approaches include selected targeted therapies for each unique subtype.

The IM subtype comprises approximately 25% of all TNBC and is characterized by an elevated expression of genes involved in immune cell signaling such as T-cell function, immune transcription and interferon response (Lehmann 2014). Furthermore, the IM subtype exhibits a substantially higher content of tumor infiltrating lymphocytes (TILs) as well as tumor associated macrophages (TAMs) than other TNBC subtypes (Mahmoud 2012 and Vinayak ASCO 2014). The clinical course of IM seems more favorable with significantly longer time to relapse compared to other TNBC subtypes (Teschendorff 2007, Lehmann 2011).

Forty percent of TNBC have high tumor infiltration of TAMs (TAM high) (Yuan 2014). The TAM high subset is enriched for IM, capturing 75% of all IM.

Figure 1-1 Triple negative breast cancer



Forty percent of TNBC patients are TAM high. Seventy-five percent of IM are found within the TAM high category. (Lehmann 2011 and Yuan 2014).

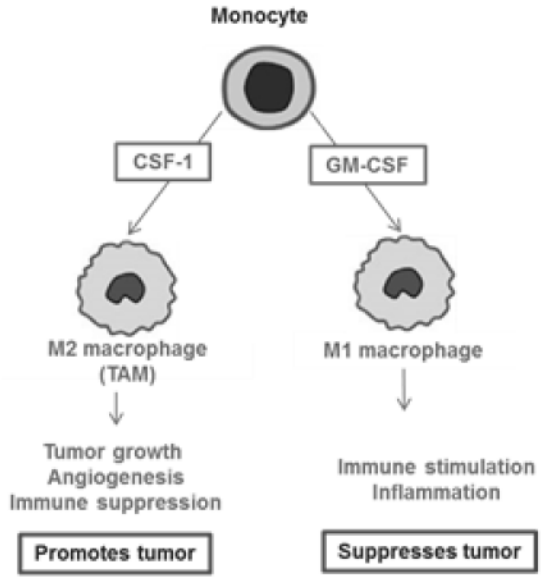
1.2 Overview of the role of the immune system in breast cancer

1.2.1 Tumor associated macrophages in breast cancer

The tumor microenvironment plays an important role in breast cancer progression. Among the many cell types associated with the tumor microenvironment, TAMs are the most influential for breast cancer progression by promoting angiogenesis, tumor growth and dissemination (Leek 1996, Pollard 2004, Obeid 2013). Furthermore, TAMs have an immunosuppressive effect by inhibiting the CD8+ cytotoxic T-cells (Noy 2014). High tumor infiltration of TAMs is associated with poor chemotherapy response and prognosis in breast cancer (DeNardo 2011, Yuan 2014).

Macrophages are differentiated into two main groups: the M1 and M2 macrophages. M1 macrophages have an important role of the immune system by protecting against tumor cells whereas M2 macrophages promote tumor growth. TAMs are defined as M2 macrophages with potent immunosuppressive functions (Mantovani 2002). Macrophages are polarized into TAMs by stimulation of macrophage colony stimulating factor (M-CSF, CSF-1) or steroids (Jaguin 2013, Obeid 2013). See Figure 1-2.

Figure 1-2 Macrophage polarization and function



CSF-1 stimulation polarizes macrophages into TAMs, thus promoting tumor growth, angiogenesis and immune suppression (Tacke 2006, Jaguin 2013, Mantovani 2002).

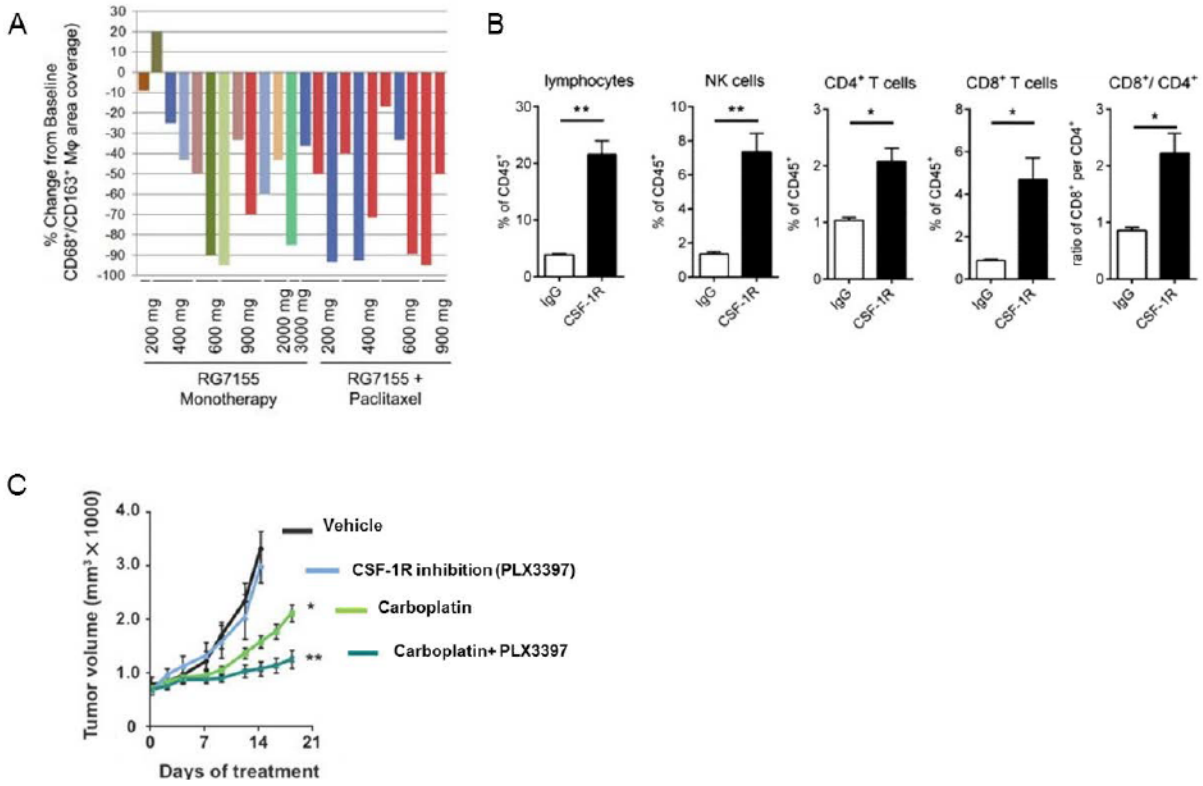
1.2.2 Immunomodulation and chemotherapy response in breast cancer

Traditionally, breast cancer has not been regarded as an immunogenic tumor type. However, today the interaction between immune cells and tumor cells is acknowledged as critical for its development and progression (de Visser 2006).

Chemotherapeutic agents mediate their anticancer activity not only by direct cytotoxic anticancer activity, but also through induced immunogenic response (Ghiringhelli 2009, Denkert 2010, Mattarollo 2011). Immune activation is commonly evaluated by assessing TILs or CD8+ T-cells (Loi 2013, Denkert 2014). The presence of TILs at diagnosis correlates with pathological response, disease free interval and overall survival after neoadjuvant/adjuvant chemotherapy, particularly in TNBC and HER2+ BC where TILs are most frequently found (West 2011, Loi 2013, Adams 2014).

Thus, improved efficacy from chemotherapy should be achieved by simultaneous activation of the immune system. This concept has been supported by a preclinical mouse model where concomitant carboplatin and TAM depletion (CSF-1R blockade) lead to enhanced response and a clinical study in which tumor biopsies from patients treated with a CSF-1R antibody displayed TAM depletion as well as activated T-cell composition (CD8+/CD4+ ratio) (DeNardo 2011, Ries 2014).

Figure 1-3 CSF-1R inhibition leads to TAM depletion, increased TILs and enhanced chemotherapy response



(A) Therapy with CSF-1R antibody as single agent or combined with paclitaxel leads to TAM depletion. The concept was studied using multiple dose levels in various solid tumors (depicted above in different colors) (Ries 2014). (B) CSF-1R inhibition increases the lymphocyte infiltration (TILs) in mice with MC38 colon cancer xenografts (Ries 2014) (C) CSF-1R inhibition enhances response to carboplatin in mice with orthotopic PyMT (breast cancer) xenografts (DeNardo, 2011).

1.3 Introduction to investigational treatment(s) and other study treatment(s)

1.3.1 Overview of MCS110

MCS110 is a high-affinity, humanized monoclonal antibody directed against human macrophage colony stimulating factor (M-CSF; also known as colony-stimulating factor-1 [CSF-1]). CSF-1 binds to the receptor tyrosine kinase CSF-1R (CSF-1 Receptor) to drive the differentiation, migration and survival of tissue macrophages. MCS110 neutralizes multiple forms of human CSF-1 and inhibits their effect on monocytes and macrophages. See IB (Investigator's Brochure) for additional preclinical data.

1.3.1.1 Non-clinical experience

1.3.1.1.1 Non-clinical pharmacology

***In vitro* pharmacology**

In vitro, the ability of MCS110 to neutralize the activity of CSF-1 was established using two different assays. The first assay involved CSF-1-dependent proliferation of the mouse myelogenous leukemia cell line M-NFS-60. This cell line responds to various recombinant forms of CSF-1, as well as CSF-1 forms present in serum, in medium conditioned by tumor cell lines, and on the cell surface. MCS110 potently inhibited the proliferation of M-NFS-60 cells in response to all human forms of CSF-1 tested. Cell proliferation in response to 10 ng/mL recombinant human CSF-1 could be completely blocked by MCS110. MCS110 blocks the activity of cynomolgus CSF-1 but has no ability to neutralize recombinant mouse CSF-1. The second assay, *in vitro* osteoclastogenesis, was set up to reflect the principal *in vivo* function of CSF-1: regulation of the survival, proliferation and differentiation of cells of the mononuclear phagocyte lineage. MCS110 induced potent inhibition of the osteoclastogenesis process as well as the morphological changes associated with the differentiation into osteoclasts.

***In vivo* pharmacology**

Given (a) the lack of activity against mouse CSF-1, and (b) the likely immune response that would develop with long-term dosing of mice with a humanized monoclonal Antibody (mAb), *in vivo* efficacy studies in human tumor cell xenograft models were conducted using two surrogate mAbs rather than MCS110 itself. These two surrogate mAbs were 5A1, a rat monoclonal IgG1antibody which neutralizes mouse (host) CSF-1, and 5H4, a mouse monoclonal IgG1 antibody which neutralizes human (tumor-derived) CSF-1. Using a combination of these two mAbs, inhibition of tumor-induced osteolysis was demonstrated in mice injected intratibially with a human breast cancer cell line (MDA-MB-231Luc). Treatment with a combination of neutralizing antibodies directed against both the host mouse source of CSF-1 and human tumor-derived CSF-1 had the lowest mean osteolytic score and a reduced number of individual animals with clearly evident bone lesions.

To evaluate the competence of TAMs for signaling via the CSF1/CSF1R pathway, macrophages from spontaneous tumors arising in MMTV-PyMT mice were analyzed for CSF1R expression by flow cytometry. $CD45^{+}CD11b^{+}F4/80^{+}$ positive TAMs stained positively for CSF1R while $CD45^{-}$ tumor cells showed no expression of the receptor. The functional dependence of TAMs on signaling mediated by the CSF1/CSF1R pathway was assessed after 6 days of treatment with the 5A1 Anti MCSF antibody to show a significant reduction in macrophages ($CD45^{+}CD11b^{+}F4/80^{+}$ cells) suggesting a functional interdependency between CSF1 and CSF1R in regulating TAMs in this breast cancer model (Strachan 2013).

1.3.1.1.2 Non- clinical pharmacokinetics and pharmacodynamics

The preclinical pharmacokinetics (PK) and pharmacodynamics (PD) of MCS110 were evaluated in cynomolgus monkeys following single intravenous (i.v) bolus injection of 0.2, 2

or 20 mg/kg, or multiple weekly iv bolus injections of 10 mg/kg for 3 weeks and 2, 20 or 100 mg/kg for up to 13 weeks. Free MCS110 (unbound to target CSF-1) exhibited dose-dependent PK, with decreasing clearance (CL) and increasing mean residence time (MRT) or effective t1/2 when dose increased. The PK profiles of free MCS110 were notably nonlinear at concentrations below approximately 20 µg/mL, presumably due to target-mediate disposition. In the 13-week study, 2 out of 22 animals tested had anti-drug antibodies detected in serum, which correlated with lower MCS110 exposure at the corresponding time points. For PD, time and dose dependent increase in total CSF-1 was observed in the 13-week study following MCS110 administration, presumably due to slower clearance of the CSF-1 after it formed immune complexes with MCS110, indicating target engagement. Decreases in other downstream biomarkers such as circulating monocytes and serum NTx were also observed following MCS110 administration.

1.3.1.1.3 Non-clinical toxicology

The cynomolgus monkey was selected as the relevant species for toxicology studies because MCS110 showed similar functional activity against cynomolgus monkey and human CSF-1 in *in vitro* bioassays. In cynomolgus monkey studies there were no severe toxicological effects in any animal given MCS110 intravenously as a single dose or as multiple doses once weekly up to 13 weeks and up to doses of 100 mg/kg, showing good tolerability of MCS110 given systemically. Mild increases in liver enzymes were seen in all studies without histopathological correlates, which resolved with clearance of the drug. This included consistent mild/moderate, dose-dependent increases in lactate dehydrogenase (LD), mild increases in AST, and minimal increases in gamma-glutamyl transpeptidase (GGT) and ALT. All parameters returned to baseline levels with the clearance of MCS110 from the serum. The most likely cause of these increases is reduced clearance rate of the serum enzymes due to the diminished numbers of Kupffer cells in the liver. This was demonstrated in cynomolgus monkey study with a single intravenous dose of MCS110, which showed a decreased clearance of histidine-tagged creatine kinase injected in parallel to MCS110. After 13 weekly doses, minimal or mild interstitial edema was seen in multiple organs histopathologically in all dose groups, including the low-dose group. Although periorbital swelling was observed to occur sporadically in all groups (including controls), the increased incidence and severity of periorbital swelling observed at 100 mg/kg suggested a relationship of this effect to MCS110 administration. No interstitial or periorbital edema was present at the end of the recovery period showing the reversal of this effect. All other effects seen, such as bone morphology changes and monocyte depletion were due to the expected pharmacological effects of MCS110. The data support the intravenous use of MCS110 in clinical trials at the doses selected (Section 2.3.2).

1.3.1.2 Clinical experience

Three clinical trials with MCS110 have been initiated.

Table 1-1 Clinical trials with MCS110

Trial	Study type	Study objectives	Patients	MCS110 dose range and schedule
MCS110A2101 Closed	First in human, dose escalation	MTD, safety, PK/PD, preliminary efficacy	Prostate cancer with bone metastases, n=3	0.01mg/kg every 14 days
MCS110X2101 Completed	Healthy volunteers, dose escalation	MTD, safety, PK/PD	Healthy, n= 52	0.01-20 mg/kg, 1-2 iv infusions every 21-56 days
MCS110X2201 Ongoing	Efficacy study	Safety, tolerability, PK/PD, efficacy	Pigmented Villonodular Synovitis (PVNS), n=16	10 mg/kg, 1-4 iv infusions every 28 days

Brief information on clinical experience of MCS110 will be provided below. For additional information, please refer to the Investigator's Brochure (IB).

1.3.1.2.1 CMCS110A2101, a first in human clinical trial

CMCS110A2101 was a first in human study in prostate cancer with bone metastases, designed to evaluate safety, tolerability and MTD of MCS110. MCS110 was administered at doses 0.01 mg/kg repeated every 2 weeks in a 28 day cycle for a total of 3 cycles. The study was closed after 3 patients due to prioritization within Novartis. No MTD was established.

Clinical safety and tolerability

MCS110 was well-tolerated and all patients completed the 3-cycle treatment. The only adverse event suspected to be related to MCS110 was an infusion reaction with chills (Grade 1), dizziness (Grade 2) and hypotension (Grade 2). The infusion reaction started 1 hour after completing the first infusion and lasted for 1 hour. No infusion reactions were noted following subsequent infusions for the same patient or in the two other patients. No DLTs were reported among the 3 patients treated with MCS110.

Clinical pharmacokinetics

Formal PK analysis was not conducted due to small number of serum samples with measurable concentrations. Following biweekly iv infusion of 0.01 mg/kg MCS110 to 3 patients, Cmax of free MCS110 was observed at 5 minutes post the end of infusion, with median of 219 and 106 ng/mL during the first and sixth infusion, respectively. Free MCS110 serum concentration decreased rapidly and was only measurable up to 2 hours after infusion in the majority of samples. No accumulation was observed at this dose level. Immunogenicity was assessed in all patients, and anti-MCS110 antibodies were not detected.

Clinical pharmacodynamics

No consistent changes in monocyte count were observed in the 3 patients treated. All patients' peripheral monocytes were within 70% of baseline levels throughout the study.

Clinical efficacy

Biologic activity of MCS110 was not observed. No consistent direction of change was seen in bone markers.

1.3.1.2.2 CMCS110X2101, a clinical trial in healthy volunteers

CMCS110X2101 was a phase I study designed to evaluate safety, tolerability and MTD of MCS110 in 52 healthy volunteers (HV). MCS110 was delivered to 27 HV at increasing single doses from 0.01-20 mg/kg. Additionally, 6 HV received 2 doses (5 mg/kg) given 21 days apart, and another 6 received 2 doses (10 mg/kg) given 56 days apart.

Clinical safety and tolerability

Asymptomatic and reversible creatine kinase (CK) elevations were seen in 15 of 52 HV. The CK elevation did not appear to reflect muscle damage since neither troponin T (marker for cardiac muscle damage) nor aldolase (marker for skeletal muscle tissue damage) was elevated. The CK elevations are thought to be caused by the pharmacological effect of MCS110.

Mild periorbital edema, was observed in 4 of 52 HV and was transient, lasting between 2 and 158 days. None of the subjects who presented with periorbital edema had developed anti-drug antibodies. The dose limiting toxicity was identified at 20 mg/kg, based on CK elevations exceeding more than 5 times the upper limit of normal. The recommended dose for future studies was set at 10mg/kg.

Clinical pharmacokinetics

Following intravenous administration of MCS110 in healthy volunteers, serum free MCS110 exhibited concentration/dose-dependent PK, with decreasing CL (clearance) and increasing MRT (mean residence time) or effective t1/2 when doses increased from 0.01 to 20 mg/kg across 8 dose levels. The shape of the serum free MCS110 PK profiles indicated target mediated disposition, where the MCS110 concentration declined more rapidly at concentrations lower than approximately 10 µg/mL. This was presumably due to binding of MCS110 to the target, suggesting that serum free MCS110 concentrations above approximately 10 µg/mL is required to saturate circulating CSF-1. At the 10 mg/kg single dose level, MCS110 concentrations were maintained above 10 µg/mL for up to 42 days post-dose. As expected, total CSF-1 exhibited dose-dependent increase in plasma following MCS110 treatment, presumably due to slower clearance of CSF-1 after it formed immune complexes with MCS110, indicating successful target engagement. The total CSF-1 concentration reached plateau at the single-dose level at or above 10 mg/kg, and it maintained at the plateau for at least 42 days at the 10 mg/kg dose.

Clinical pharmacodynamics

Expected pharmacological responses were observed in downstream biomarkers including dose-dependent decreases in circulating CD14+ or CD14+CD16+ monocytes and C-terminal telopeptide of type I collagen (CTX-1), a bone resorption marker. In addition, dose-dependent increases in CK were observed. Simulation of steady-state dose-response relationships for biomarkers showed that with the once-every-4 week (Q4W) iv administration of MCS110, the response of PD biomarkers (CD14+ and CD14+CD16+ monocytes, and CTX-1) was expected to be close to maximal at the doses at or above 5 mg/kg and minimal at doses at or below 1 mg/kg.

1.3.1.2.3 CMCS110X2201, a phase II study in pigmented villonodular synovitis

CMCS110X2201 is an ongoing phase II study designed to evaluate safety, tolerability and efficacy with MCS110 in pigmented villonodular synovitis (PVNS). PVNS is a benign tumor consisting of macrophages and multinucleated giant cells, most commonly located to joints. Five patients were enrolled in the first part of the study (Part A) with single injections (10 mg/kg) and 11 are planned to participate in the repeat-dose study (Part B) with 4 injections of MCS110 (10mg/kg) repeated every 28 days.

Clinical safety and tolerability

As of August 2014, the preliminary data on reported AEs, with suspected relation to the drug, include the following: knee arthralgia, CK elevation, amylase elevation (all of moderate grade), and influenza symptoms, lipase elevation, AST/GGT elevation, hypotension and edema (all of mild grade).

Clinical pharmacokinetics

PK analysis is ongoing. Preliminary data of the first 3 patients with single iv infusion of 10 mg/kg in the ongoing study suggested similar PK as in HV.

Clinical pharmacodynamics

Preliminary data from the ongoing study in PVNS patients showed an expected decrease in monocytes and CTX-1, while an increase was seen in CK. Maximum values are generally observed at Day 28 or Day 43 and then returning back to baseline.

Clinical efficacy

One single injection (10 mg/kg) resulted in significant (30-50%) tumor reductions (MRI) in all (4) patients receiving the drug.

1.3.2 Overview of carboplatin

Carboplatin is an alkylating agent which acts by producing cross-linking guanine bases in DNA double-helix strands, thereby preventing transcription and replication. The mechanism of action is not cell-cycle specific (McEvoy 2000).

The major route of elimination of carboplatin is renal excretion. Patients with normal renal function excrete 71% of the dose within 24 hours. Drug interactions with aminoglycosides, phenytoin and warfarin have been reported and concomitant use is cautioned (McEvoy 2000).

The main toxicities of carboplatin are myelosuppression, nausea/vomiting, nephrotoxicity and peripheral neuropathy. Hypersensitivity reactions have been reported, particularly when used in combination or after repeated exposure (McEvoy 2000, Markman 1999).

Carboplatin is approved for use alone or combined with other drugs in ovarian cancer and non-small lung cancer, but widely used also in other malignancies such as head neck cancer, germ cell tumors, breast cancer and others. Numerous dosing schedules exist and depend on disease, response expectations and concomitant therapy (NCCN 2014, ESMO Guidelines 2014).

1.3.3 Overview of gemcitabine

Gemcitabine is a pyrimidine analog which is metabolized to two active metabolites, gemcitabine diphosphate and gemcitabine triphosphate. The cytotoxic effects of gemcitabine are exerted through incorporation of gemcitabine triphosphate into DNA, resulting in inhibition of DNA synthesis and induction of apoptosis. Gemcitabine is cell-cycle phase specific (S and G_1/S-phases) (Grindey 1990, Eli Lilly 1999).

Gemcitabine is rapidly metabolized by cytidine deaminases in liver, kidney, blood and other tissue (Gilbert 2006). Drug elimination is mediated mainly through renal excretion. Within one week of administration 92% to 98% of the dose was recovered, almost entirely in the urine (Eli Lilly 1999).

The main toxicities of gemcitabine are elevated liver enzymes [aspartate transaminase (ASAT)/ aspartate aminotranferase (ALAT)] and anaplastic lymphoma kinase (ALK), nausea/vomiting, protein/hematuria, dyspnea, rash and myelosuppression (Moore 1992, Mertens 1993, Lund 1994).

Gemcitabine is approved for use alone or with other drugs in pancreatic cancer, ovarian cancer, non-small lung cancer and breast cancer. The most commonly used schedule for gemcitabine is administration on days 1 and 8 of each 21-day cycle, but there are several options (NCCN 2014, ESMO Guidelines 2014).

1.4 Overview of combination treatment

1.4.1 Non-clinical

No preclinical data exist for the combination of MCS110 with carbo/gem. However, preclinical data from other compounds targeting the CSF-1/CSF1R signaling pathway in combination with chemotherapy (carboplatin, paclitaxel) supports the study concept of this trial (DeNardo 2011). See Section 2.1.

1.4.2 Clinical

The study started enrollment in August 2015. After the enrollment halt in June 2017, LPFT occurred on July 17th, 2017. Thirty-four patients have been treated with MCS110 at 10 mg/kg Q3W (with or without an additional dose of MCS110 on C1D8) in combination with carbo/gem.

The most common adverse events observed suspected to be related to MCS110 are periorbital edema, elevated creatine kinase and elevated liver enzymes. For additional information, please refer to the MCS110 Investigator's brochure.

After the first early safety review meeting in May 2016, it was decided to remove the additional dose of MCS110 10 mg/kg on C1D8 in order to improve tolerability. No immediate safety concerns with the current dosing were identified.

An additional Safety review meeting took place in May 2017. Safety data indicated that the dosing regimen of MCS110 10 mg/kg without the additional dose on C1D8 was better tolerated regarding AEs and dose delays/interruptions than the regimen including an

additional C1D8 dose. Thus, the established dosing regimen for MCS110 in combination with carbo/gem is 10 mg/kg Q3W.

In addition, clinical data from a trial combining CSF-1R blockade (antibody) with paclitaxel demonstrated robust TAM depletion. No data was provided for anti-tumor activity or toxicity. (Ries 2014). See Section 2.1.

1.4.3 Potential for drug-drug interactions

Specific studies to investigate drug-drug interactions (DDI) have not been conducted with MCS110. Antibodies that modulate cytokines, which may regulate cytochrome P450 (CYP) enzymes, may cause DDI with small molecule drugs because of the potential to alter CYP-mediated metabolism (Lee et al 2010; Huang et al 2010). However, MCS110 specifically neutralizes CSF-1 and hence, it is not expected to modulate cytokines. In addition, as an antibody, MCS110 is eliminated through protein catabolism and target-mediated disposition. Therefore, MCS110 is not anticipated to be directly eliminated through hepatic/renal metabolism and excretion, to compete with the elimination of carbo and gem, which are mainly eliminated through metabolism (gem) and renal excretion (gem and carbo). Therefore, the risk of DDI between MCS110 and carbo or gem is anticipated to be low. Nevertheless, PK of carbo and gem in the presence and absence of MCS110 will be characterized in this study to assess the DDI, if any, between MCS110 and carbo or gem (Section 10.5.3).

1.4.4 Expected overlapping toxicities

Asymptomatic and transient CK elevations were frequently seen in clinical studies with MCS110. Transient increases of Grade 1-2 AST were observed as well, whereas ALT elevations were only seen in occasional patients. The increase of enzymes does not appear to reflect muscle damage since markers for cardiac or skeletal muscle damage were evaluated and found normal. Furthermore, isolated CK/AST elevation is not consistent with liver damage (Krishnamurthy 2009). The elevation of enzymes is considered a pharmacological effect of MCS110 reducing the number of liver macrophages (Kupffer cells), leading to reduced clearance rate.

Grade 1-2 elevations of AST/ALT are commonly seen during treatment with gemcitabine, whereas Grade 3-4 toxicity is rare. However, these increases are seldom of clinical significance and there is no evidence of increasing hepatic toxicity with either longer duration of gemcitabine treatment or cumulative dose (Aapro 1998 and Eli Lilly 1999). FDA approved prescribing information does not recommend any dose modifications of gemcitabine unless Grade 3-4 liver toxicity is reported, at which 50% dose reduction or withholding of the drug is proposed.

Even though ALT elevation is rare with MCS110 it is frequently seen with administration of gemcitabine. Due to the potential risk of overlapping liver enzyme elevations, only patients with normal liver function and without known chronic liver or heart disease are eligible for enrollment. See Section 5.2. Furthermore, patients will be carefully monitored regarding their liver enzymes during the study and instructions for dose modifications are provided. See Section 6.2.1.1.

2 Rationale

2.1 Study rationale and purpose

No substantial progress has been made in the treatment of TNBC and the prognosis remains poor (Foulkes 2010). Currently, chemotherapy is the only treatment option. Although TNBC is a chemosensitive disease and a subset of chemo responders has an excellent prognosis, the majority of patients rapidly relapses (Liedtke 2008). Current treatment strategy in TNBC aims at further improving the efficacy of chemotherapy.

Preclinical and clinical data suggest that TNBC is a highly immunogenic solid tumor and that immunomodulation may lead to enhanced chemotherapy response and improved patient outcome. CSF-1R inhibition leads to increased lymphocyte infiltration and enhanced response to carboplatin in xenograft models (DeNardo 2011 and Ries 2014). Furthermore, TAM depletion is achieved in patients treated with CSF-1R directed therapy (Ries 2014) (Section 1.2, Figure 1-3). Randomized phase III trials show that adding carboplatin to standard chemotherapy significantly increases the response rate in TNBC, particularly in those with high amounts of TILs (Vinayak 2014, von Minckwitz 2014).

The targeted study population will include patients whose tumors contain high immunological infiltrates of TAMs (TAM high). A recent publication identified 40% of TNBC as TAM high and demonstrated that TAM high had a significantly worse outcome than TAM low (Yuan 2014). The assessment of TAM content will be obtained through submission of samples to a Novartis designated laboratory where IHC for CD163 (marker of TAM) will be performed. The selection strategy is expected to identify approximately 40% of TNBC patients as TAM high and enriched for the IM subtype (Lehmann 2011 and Yuan 2014). (Section 1.1.1).

The purpose of this study is to determine if depletion of TAMs induced by MCS110 improves the response to the chemotherapeutic agents carboplatin and gemcitabine (carbo/gem).

2.2 Rationale for the study design

This study is a phase II, open-label, randomized study of MCS110 in combination with carbo/gem (Arm 1) versus carbo/gem alone (Arm 2) in patients with advanced TNBC. The study will target TNBC patients with TAM high tumors with no prior chemotherapy in the advanced setting.

The two-arm study is designed to provide a preliminary comparison of the clinical efficacy as well as safety and tolerability between the two treatment combinations (Arm 1 vs Arm 2). Historical data on efficacy and safety are available for the chemotherapy regimen in metastatic TNBC, but not for the targeted patient population (IM) which may have a more favorable prognosis. A randomized study design was selected to allow for evaluation of the potential clinical benefit of adding MCS110 to carboplatin/gemcitabine in this particular subset of TNBC.

The study design includes one or more early safety reviews. The first safety review meeting will be performed after the first 9 patients have received 2 cycles of either MCS110 + carbo/gem or carbo/gem alone, or discontinued earlier due to an adverse event. If the dosing regimen is changed at this time, an additional safety review will take place after 9 patients

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

Novartis clinical team and study investigators will evaluate clinical, PK and laboratory data at a joint meeting to make an assessment of the safety of both study arms. If safety concerns are noted, then the MCS110 dose will be reduced (from 10 mg/kg to 5 mg/kg or from 5 mg/kg to 2.5 mg/kg) with or without an additional dose of MCS110 on Cycle 1 Day 8 (Section 4.1). Enrollment of additional patients will not be stopped during the safety review period.

The primary objective of this study is to evaluate the effect on clinical activity of adding MCS110 to carboplatin/gemcitabine, one of the recommended treatment options in the first-line setting for advanced TNBC. The randomized design minimizes allocation bias, balancing both known and unknown prognostic factors in the assignment of treatments. Patients will be randomized in a ratio of 2:1 (MCS110 + carbo/gem: carbo/gem) to allow for a larger proportion of patients to receive the study drug and hence an increased chance for benefit from the combination. This will also allow for sufficient patients to characterize the safety profile of the MCS110 + carbo/gem combination.

For the detailed statistical methods, refer to Section 10.

2.3 Rationale for dose and regimen selection

2.3.1 Rationale for dose and regimen for carboplatin and gemcitabine

No standard of care therapy exists for advanced TNBC. However, published data from randomized phase II and phase III trials demonstrate efficacy and tolerability using carboplatin/gemcitabine in the 1st-3rd line metastatic setting (O'Shaughnessy 2011). The doses and treatment cycles will follow the above mentioned published regimens with carboplatin (AUC 2) and gemcitabine (1000mg/m^2) administered on days 1 and 8 in 21-day cycles.

2.3.2 Rationale for dose and regimen for MCS110

In the HV study (Study CMCS110X2101), >5-fold asymptomatic CK elevation was identified with single iv infusions of MCS110 at the dose of 20 mg/kg. The recommended dose for subsequent treatment was set at 10 mg/kg where MCS110 was well tolerated. The PK and total CSF-1 concentration data suggest that circulating CSF-1 was saturated for approximately 6 weeks following a single dose of 10 mg/kg (Section 1.3.1.2.2). PD biomarker response (monocytes and CTX-1) was predicted to be close to maximal with doses at or above 5 mg/kg, based on HV data. Significant tumor volume reductions were achieved in PVNS patients (Study CMCS110X2201) using 10 mg/kg as single iv infusion. A repeat-dose phase of the study is currently ongoing to evaluate the tolerability and efficacy of 4 iv infusions of 10 mg/kg MCS110 every 4 weeks (Q4W). Preliminary data with single iv infusion of 10 mg/kg in the ongoing study suggest that the PK profile of MCS110 and circulating CSF-1 levels are similar in PVNS patients and in HV.

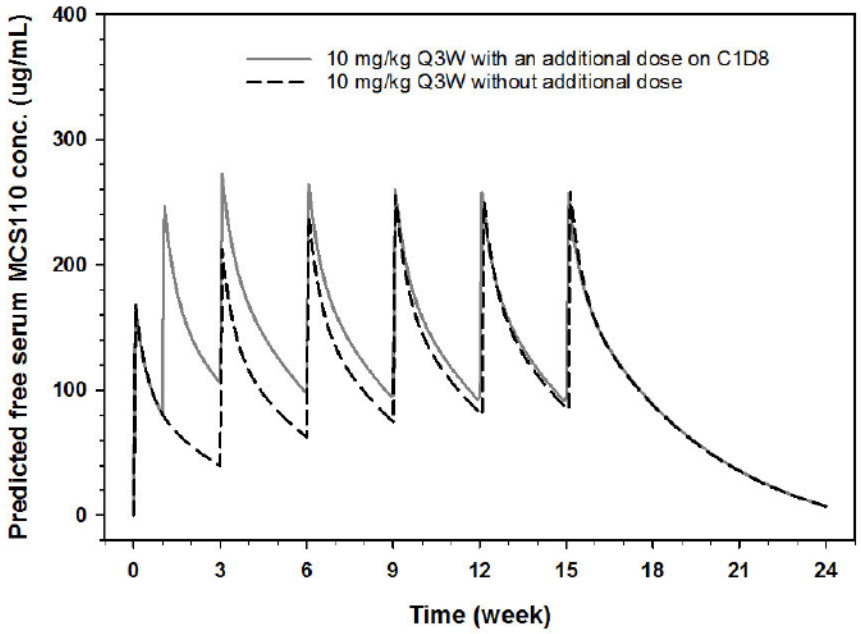
In this study, patients will receive MCS110 Q3W at a dose of 10 mg/kg iv based on safety and efficacy data in HV and PVNS patients. The 3-week cycle is chosen to coordinate with the

administration cycle of the chemotherapy (carbo/gem). In addition, compared to the 4-week cycle used in the ongoing study of PVNS patients, the 3-week cycle may improve treatment benefit due to potentially higher CSF-1 levels in TNBC patients than in HV or PVNS patients.

All patients will receive an additional 10 mg/kg dose of MCS110 on Cycle 1 Day 8. The rationale for adding an additional dose is to reach steady state earlier, thus achieving a faster and more continuous inhibition of CSF-1. In preclinical models continuous inhibition of the CSF1-R pathway is essential to maintain efficacious TAM depletion as an anticancer therapy (Strachan 2013).

MCS110 concentrations are predicted to reach steady-state at Week 6 instead of Week 12 with an additional dose on Cycle 1 Day 8, based on the population PK model developed from HV data (Figure 2-1). Achieving a faster TAM depletion and, thus enhanced chemotherapy efficacy may be of clinical importance in TNBC given the aggressive clinical course.

Figure 2-1 Predicted population mean serum concentration profiles of free MCS110 following 10 mg/kg Q3W iv infusion with and without an additional dose on C1D8



Note: Prediction is based on population PK model in Modeling & Simulation report of Study CMCS110X2101.

Following administration of 10 mg/kg Q3W of MCS110 with an additional C1D8 dose, it is predicted that Cmax will be achieved 5 weeks sooner than without the additional C1D8 dose (Figure 2-1). The Cmax and steady-state AUC of MCS110 is predicted to be approximately 2-fold lower than that observed in HV treated with a single dose of 20mg/kg single dose, and approximately 19 fold lower for Cmax and 10-fold lower for AUC than that observed in cynomolgus monkeys dosed repeatedly at 100 mg/kg (Table 2-1).

Based on clinical experience with MCS110, the short time to Cmax, and the estimated safety margins for exposure, a dose regimen of 10 mg/kg every 21 days with an additional dose on C1D8 was selected.

Table 2-1 Comparison of observed exposure in cynomolgus monkeys and healthy volunteers versus predicted exposure in CMCS110Z2201

Study	Dose regimen (iv infusion)	AUC (µg*day/mL)	C_{max} (µg /mL)	Exposure margin[a]			
				Relative to monkey AUC $_{7day,ss}$	Relative to HV AUC_{0-inf}	Relative to monkey C_{max}	Relative to HV C_{max}
13-week toxicology (cynomolgus monkey)[b]	100 mg/kg QW	29025 ($AUC_{7day,ss}$)[c]	5156	-	-	-	-
CMCS110X2101 (HV)[d]	20 mg/kg single dose	6450 (AUC_{0-inf})	446	-	-	-	-
CMCS110Z2201 (Predicted data)[e]	10 mg/kg Q3W with an additional dose of 10 mg/kg on C1D8	2896 ($AUC_{0-21day, C1}$)	272	10	2.2	19	1.6
		2998 ($AUC_{21day,ss}$)		9.7	2.2		

ss: steady state, AUC_{0-inf}: AUC from time zero to infinity; $AUC_{7day,ss}$: AUC from time zero to 7 days during steady state $AUC_{0-21day, C1}$: AUC from time zero to 21 days during Cycle 1; $AUC_{21day,ss}$: AUC from time zero to 21 days during steady state.
[a] Mean observed exposure in monkey or HV divided by mean predicted exposure of CMCS110Z2201
[b] Data are from preclinical safety study report of 13-Week GLP study in cynomolgus monkeys.
[c] Average of mean male and female Day 85 $AUC_{0-tlast}$ of non-recovery animals from start of infusion to the last measured sampling time point (7 day)
[d] Data are from clinical study report of Study CMCS110X2101.
[e] AUC and Cmax calculated using population mean concentration profile simulated by the population PK model from Modeling & Simulation report of Study CMCS110X2101.

2.4 Rationale for choice of combination drugs

Carbo/gem was chosen as one of several treatment regimens used in advanced TNBC. A low-moderately emetogenic dosing regimen will be used, which affords the advantage of little or no steroids, a treatment that could potentially activate TAMs (Section 1.2.1). In preclinical models, carboplatin combined with TAM depleting drugs lead to enhanced chemotherapy response (DeNardo 2011)

2.5 Rationale for choice of comparators drugs

Carbo/gem has a documented high efficacy in metastatic TNBC and is one of the recommended treatment options in the first-line metastatic setting (O'Shaughnessy 2011, NCCN 2014, ESMO 2014).

3 Objectives and endpoints

Objectives and related endpoints are described in Table 3-1 below.

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
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)	
Secondary		Refer to Section 10.5
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 10.5.2
Characterize PK of MCS110 when combined with carbo/gem	Serum concentration of free MCS110 and derived PK parameters	Refer to Section 10.5.3
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 10.5.3
Characterize PD effect of MCS110 when combined with carbo/gem	Total CSF-I circulating levels, serum CTX-I and circulating monocytes in blood. TAM and TIL content in pre- and post-dose tumor biopsies	Refer to Section 10.5.4
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 10.5.1

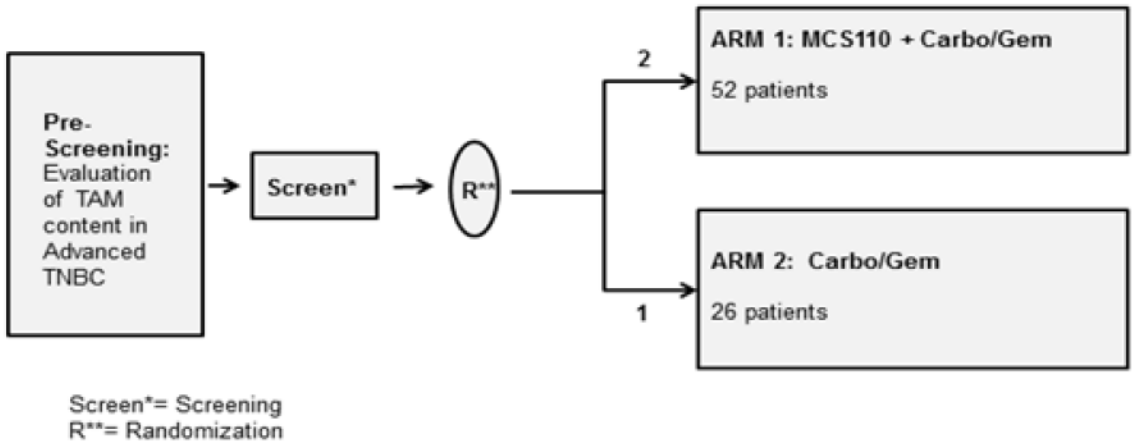
[redacted]

4 Study design

4.1 Description of study design

This is a phase II, randomized (2:1), two-arm, open-label multi-center, study of patients with advanced TNBC (Section 5.2).

Figure 4-1 Overview of study design



An early safety review meeting will take place when 9 patients have been randomized and completed 2 cycles of either MCS110 + carbo/gem or carbo/gem alone, or discontinued earlier due to an adverse event. If the dosing regimen is changed at this time, an additional safety review of the new dosing regimen will take place after 9 patients have been randomized and completed 2 cycles of MCS110 (per the new dosing regimen) + carbo/gem or carbo/gem alone, 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 (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 5 mg/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 (see Section 8.5).

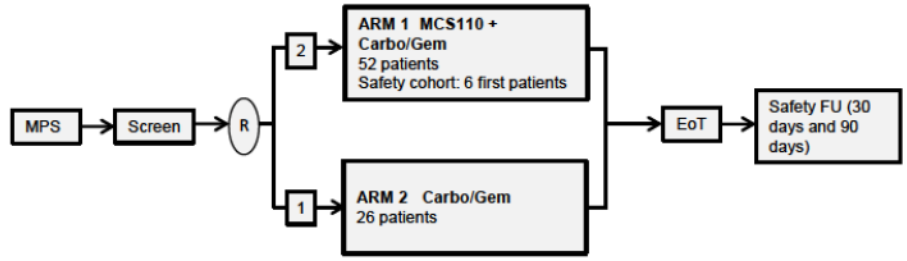
Once a dosing regimen is agreed upon after the safety review meeting(s), all the subsequent patients randomized to Arm 1 will receive the confirmed dose. The study will continue until

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 since recruitment continues during the decision making.

If the decision has been taken to change the MCS110 dosing regimen at the safety review meeting, patients who are in the screening phase at the time of the decision and eligible for enrollment must receive the new dosing regimen of MCS110. Patients who have already received their first dose of treatment at the time of the decision will keep their initial treatment regimen.

Figure 4-2 Study visit flow



MPS = Molecular pre-screening
Screen = Screening
R= Randomization
EoT = End of treatment
FU = Follow-up

Patients will undergo clinical and laboratory assessments during screening/baseline and periodically during treatment as outlined in Table 7-1.

For study visit flow detailed information is provided on Section 7.1.

4.2 Definition of end of the study

End of study will be upon the last patient's completion of safety follow-up (see Section 7.1.6).

4.3 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1.4 for a discontinued or withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

Women with advanced (metastatic or locally advanced BC not amenable to curative treatment by surgery or radiotherapy) TNBC will be considered for participation in this study. All patients will have a newly obtained tumor sample taken from an appropriate tumor site at the pre-screening visit. The tumor sample will be assessed regarding TAM content. Only patients whose tumors have a high content of TAMs will be enrolled in the treatment part of the study.

The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

Patients eligible for inclusion in this study have to meet **all** of the following criteria:
Written informed consent must be obtained prior to any screening procedures.

1. Adult women (≥ 18 years of age) with advanced TNBC.
2. Histological or cytological evidence of estrogen-receptor negative (ER-), progesterone receptor negative (PgR-) and human epidermal growth factor-2 receptor negative (HER2-) BC by local laboratory testing, based on last available tumor tissue.
   - ER/PgR negativity to follow local guidelines
   - If IHC HER2 2+, a negative FISH test is required
3. A pre-treatment tumor biopsy demonstrating high TAM content as assessed per the central laboratory
4. Radiological or objective evidence of recurrence or progression prior to enrollment
5. Patients must have:
   - At least one measurable lesion per RECIST 1.1. (Note: Measurable lesions include lytic or mixed (lytic + blastic) bone lesions, with an identifiable soft tissue component that meets the measurability criteria)
     or
   - Bone lesions: non-measurable lytic or mixed (lytic +blastic) in the absence of measurable disease as defined above. Patients with only non-measurable lesions (e.g. pleural effusion, ascites) and no lytic or mixed bone lesions are not eligible.
6. ECOG Performance Status 0-2
7. Patients must sign informed consent before any study-specific molecular pre-screening and screening procedures

5.3 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Prior chemotherapy for advanced BC. Previous adjuvant/neoadjuvant chemotherapy is allowed (carboplatin, cisplatin or gemcitabine only if > 12 months has passed since last administration).

   Note: A chemotherapy line only counts if being given for ≥ 21 days.

2. Known hypersensitivity to carboplatin, cisplatin, gemcitabine, MCS110 or other monoclonal antibodies. Another malignancy within three years prior to signing of informed consent, with the exception of adequately treated in situ carcinoma of any type, basal or squamous cell skin cancer, and any malignancy considered to be indolent and that has never required therapy. Patients with a stable malignancy may be considered for inclusion after discussion with the sponsor
3. Patients with a primary CNS tumor or CNS tumor involvement. However, patients with metastatic CNS tumors may participate in this study if the patient is:
   - Neurologically stable
   - Does not require steroids
   - Has recovered from local treatment such as radiation and/or surgery.
4. Therapy for underlying malignancy within 2 weeks prior to start of study treatment:
   - Chemotherapy, biologic therapy (antibodies and biologically targeted small molecules)
   - Radiotherapy
   - Major surgery
5. Presence of ≥ CTCAE grade 2 toxicity (except alopecia due to prior cancer therapy).
6. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids (≥10 mg of prednisone or equivalent) at the time of first dose of study drug.
7. Severe and / or uncontrolled medical conditions that in the investigator's opinion could affect the safety of the individual or impair the assessment of study result.
8. Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening.
9. Known history of human immunodeficiency virus or active infection with hepatitis virus or any uncontrolled active systemic infection.
10. Patients with the following laboratory values during screening and on Day 1 pre-dose:
    - Absolute Neutrophil Count (ANC) < $1.5x10^9$/L
    - Hemoglobin < 9 g/dL
    - Platelets < $100x10^9$/L
    - Serum creatinine > 1.5 x ULN
    - Serum total bilirubin > 1.5 x ULN
    - AST/SGOT and ALT/SGPT > 3.0 x ULN
11. Patients unwilling or unable to comply with the protocol.
12. Participation in parallel investigational drug or device studies
13. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 90 days after the last dose of MCS110 or for 30

days after the last dose of carboplatin and gemcitabine or as recommended per the local approved labels for carboplatin and gemcitabine, whichever has the longest duration . Highly Effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

6 Treatment

6.1 Study treatment

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

6.1.1 Dosing regimen

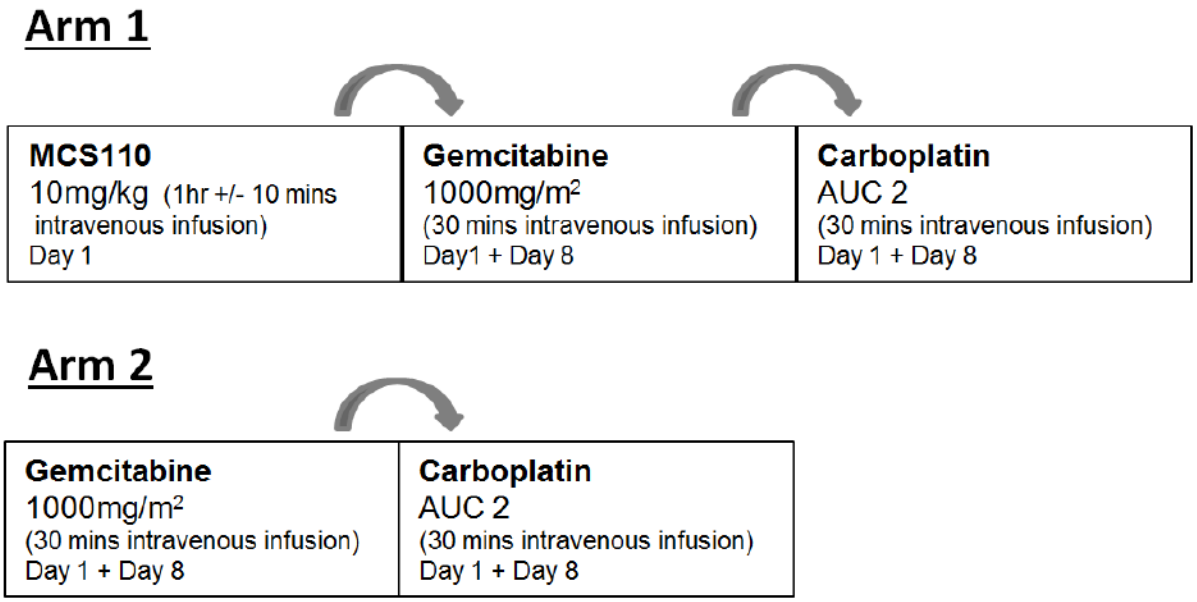
Table 6-1 Dose and treatment schedule

Study Drug & Combination treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
MCS110	Intravenous infusion	10 mg/kg ,5 mg/kg or 2.5 mg/kg	Day 1, with or without additional dose at C1D8
Gemcitabine	Intravenous infusion	1000 mg/m^2	Days 1 & 8
Carboplatin	Intravenous infusion	AUC 2	Days 1 & 8

After reviewing the clinical, PK and laboratory data obtained from the safety review meetings, the MCS110 dose may be reduced, and/or the additional dose on C1D8 may be omitted. (Section 2.2 and Section 4.1).The doses of MCS110, carbo/gem will be calculated on Day 1 at each cycle. The calculations will be based on weight for MCS110, creatinine clearance (according to institutional guidelines) for carbo and body surface area for gem.

A pharmacy manual will be provided with details about how to administer MCS110.

Figure 6-1 Study Drug Administration



6.1.2 Ancillary treatments

6.1.2.1 Ancillary treatments for MCS110

The most common side-effects from MCS110 include periorbital edema and CK elevation, both of which do not require any treatment.

Mild infusion reactions were reported in 2 patients where all symptoms (dizziness, chills, hypotension) resolved within 1 hour. One patient was re-challenged with MCS110 and did not have any infusion reactions during subsequent infusions. Patients should be monitored for hypersensitivity reactions according to local guidelines. Appropriate treatment for hypersensitivity reactions should be available at bedside and a physician readily available. Prophylaxis to prevent infusion reactions is only recommended for subsequent doses in patients who previously experienced an infusion reaction to MCS110.

6.1.2.2 Ancillary treatments for carboplatin and gemcitabine

6.1.2.2.1 Nausea

A low-dose carboplatin dosing regimen will be used with a low to moderate risk for emesis. All patients should receive anti-emetic pre- and post-medication according to local guidelines,

but steroids should be used with moderation. The total steroid dose per treatment cycle should not exceed 16 mg of dexamethasone or equivalent.

6.1.2.2.2 Hypersensitivity reactions

Hypersensitivity reactions caused by carboplatin have been reported, but are rare. Premedication to prevent hypersensitivity reactions is not recommended, but may be used per local recommendation. Prophylactic steroids should be avoided.

6.1.3 Treatment duration

Patient may continue treatment with the study drug until patient experiences unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the patient. Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue study treatment.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments and appropriate supportive therapies are permitted. The following guidelines should be followed and these changes must be recorded on the Dosage Administration Record eCRF.

The criteria for dose modifications of the study treatment for toxicities considered suspected to be related (suspected includes possibly, probably or definitely related) to the study medication treatment are outlined in Table 6-2, Table 6-3 and Table 6-4. Study treatment may be delayed by ≤ 1 week from the expected day of the next study treatment administration for any reason. If study treatment cannot be given within this time frame due to persisting toxicity, the dose should be skipped. Patients requiring a dose delay of > 3 weeks for a study treatment related toxicity should be discontinued from the study treatment. If the patient is clearly benefiting from the study treatment and in the opinion of the investigator it is in the patient's best interest to continue the study treatment, after discussion with Novartis, the patient may remain on study treatment. Patients who discontinue from the study for a study drug-related AE or an abnormal laboratory value must be followed as described in Section 8.

If, after interruption of the study treatment and resolution, the study treatment is resumed at the same dose following the criteria in Table 6-2, Table 6-3, Table 6-4 and the same toxicity reoccurs with the same or worse severity, the dose of the chemotherapy and/or MCS110 should be reduced as follows. The chemotherapy can be dose reduced by 2 dose levels; -20% and -40% of the original dose whereas MCS110 can be dose reduced by 3, 2 or 1 dose levels depending on the starting dose (from 10 mg/kg to 5 mg /kg to 2.5 mg/kg to 1 mg/kg, or from 5 mg/kg to 2.5 mg/kg to 1 mg/kg, or from 2.5 mg/kg to 1 mg/kg).

For each patient, once a dose level reduction has occurred, the dose level must not be re-escalated during subsequent treatment cycles. If more than 2 dose reductions of carbo and/or gem, or MCS110 doses below 1.0 mg/kg, are needed, the respective study drug(s) will be

discontinued. Patients who discontinued 1 or 2 drugs in the Arm 1 regimen or 1 drug only in the Arm 2 regimen due to toxicity may continue with the remainder of drugs assigned at randomization upon discussion with the Novartis Medical Monitor.

The interval of MCS110 infusion should be prolonged by up to 1 week to coordinate with any delayed chemotherapy treatment. If chemotherapy is delayed more than 1 week, but less than 3 weeks, investigators should discuss with Novartis how to re-start and coordinate treatment in the investigational treatment arm.

6.2.1.1 Dose modifications and action for toxicities suspected to be related to study treatment

Table 6-2 Dose modifications and action for toxicities suspected to be related to MCS110

Toxicity	CTCAE Grade	Action
CK elevation	Grade ≥3 (CK>5 x ULN)	Monitor CK-MB, troponin (I or T) and creatinine. • If CK-MB and troponin (I or T) are normal, creatinine ≤ 1.5 x baseline and patient asymptomatic, maintain dose level. • If CK-MB and troponin (I or T) are abnormal or creatinine (> 1.5 x baseline and > ULN) or patient symptomatic, withhold drugs and explore alternative causes for elevated CK (for example myositis and rhabdomyolysis) according to local guidelines. After recovery of CK-MB, troponin (I or T) and creatinine to Grade 1 or baseline, study treatment may be resumed: chemotherapy at previous doses and MCS110 at 50%[a] of the previous dose
Periorbital edema	Grade ≥3 (severe)	Hold MCS110. Consultation of an ophthalmologist may be considered by the investigator. After recovery to Grade 1 or baseline, MCS110 may be resumed at 50%[a] of the previous dose.
Hepatic	Grade ≥ 3 (total bilirubin >3 x ULN or ALT >5 x ULN) or total bilirubin grade ≥ 2 with ALT grade ≥ 2	Hold study treatment (including chemotherapy) until resolved to ≤ Grade 1 or baseline. After recovery study treatment may be resumed per the investigator's discretion: chemotherapeutic agents reduced by 20% and MCS110 by 50%[a] of the previous dose. End treatment and discontinue patient from study.
Infusion related reaction	Grade 1 (transient flushing or rash, drug fever<38°C/ < 100.4°F)	Slow down infusion rate to 50% of previous rate. Consider premedication at subsequent infusions with anti-histamine (diphenhydramine 50 mg or equivalent) and acetaminophen (1 g). Patients must be observed for at least 3 hours after each subsequent infusion before discharge.
	Grade 2 (flushing, rash, urticaria, dyspnea, drug fever ≥38.5°C/≥101.3°F)	Interrupt the infusion of MCS110. Administer anti-histamines or corticosteroids. After recovery of symptoms, resume infusion at a slower rate (50% of previous rate). If no further symptoms appear, complete the administration. Patients must be observed for at least 3 hours after each subsequent infusion before discharge.
	Grade 3 (symptomatic bronchospasm, w/wo urticaria[b]; allergy- related edema/ angio-edema;	Immediately stop MCS110 infusion and discontinue patient from study. Administer anti-histamines or corticosteroids. Epinephrine can be indicated when wheezing and anaphylaxis of acute life-threatening nature is present but should be

Toxicity	CTCAE Grade	Action
	hypotension[c] and Grade 4 (anaphylaxis[d])	chosen cautiously. Patients must be observed as per local guidelines before discharge.
Others (except for fatigue and alopecia)	Grade ≥ 3	Hold MCS110. After recovery to Grade ≤1 or baseline, MCS110 may be resumed at 50%[a] of the previous dose.

[a]Except for dose reductions of MCS110 dose of 2.5 mg/kg: in this case, the dose will be reduced to MCS110 1 mg/kg
[b] Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity.
[c] Defined by a systolic pressure drop ≥ 30 mm Hg
[d] Defined as vascular collapse and shock (blood pressure < 90 mm Hg, unresponsive to IV fluids) believed to be allergic in origin, with or without antecedent respiratory distress and occurring within 30 minutes of initiation of MCS110 infusion. Cutaneous manifestations include pruritus, urticaria or angioedema.

Table 6-3 Dose modifications for hematological toxicities suspected to be related to carbo/gem

Toxicity	AE	Action
Hematological toxicity[a]		
D1[b] of each cycle		
neutropenia or thrombocytopenia	ANC < $1.0x10^9$/L or platelets< $100x10^9$/L	Hold both drugs until ANC≥ $1.0x10^9$/L and platelets ≥$100x10^9$/l, then deliver treatment. *First episode:* reduce carboplatin and gemcitabine by 20% of original starting dose. *Second episode*: reduce both drugs by 40% of original starting dose.
D8[b] of each cycle		
neutropenia or thrombocytopenia	ANC 0.75 - <$1.0x10^9$/L or platelets 75 - <$100x10^9$/L	Reduce carboplatin and gemcitabine by 20% of D1 dose.
neutropenia or thrombocytopenia	ANC < $0.75x10^9$/L or platelets < $75x10^9$/L	Hold both drugs and do not make up dose.
At any other time point		
febrile neutropenia	ANC <$1.0x10^9$/l with a single temperature of >38.3 ºC (101 ºF) or a sustained temperature of >=38 ºC (100.4 ºF) for more than one hour.	*First episode:* reduce carboplatin and gemcitabine by 20% of original starting dose. *Second episode*: reduce both drugs by 40% of original starting dose.
thrombocytopenia	Platelets < 25 $x10^9$/L or platelets < 50 $x10^9$/L with bleeding	*First episode:* reduce carboplatin and gemcitabine by 20% of original starting dose. *Second episode*: reduce both drugs by 40% of original starting dose.
Others	Grade ≥ 3	*First episode:* reduce carboplatin and gemcitabine by 20% of original starting dose. *Second episode*: reduce both drugs by 40% of original starting dose.

[a]As soon as requirements for hematological parameters are reached study treatment should be delivered.
[b]Dose reductions should be performed based on D1or D8 labs, not based on nadir counts of neutrophils and platelets, unless for toxicities described under "At any other time point" above.

Table 6-4 Dose modifications for non-hematological toxicities suspected to be related to carbo/gem

Toxicity	CTC AE Grade	Action[a]
Non-hematological toxicity		
Pneumonitis	Grade≥ 2 (symptomatic, medical intervention indicated)	Discontinue gemcitabine promptly. Treatment with steroids should be initiated as per local guidelines.
Hepatic	Grade ≥ 3 (total bilirubin >3 x ULN or ALT >5 x ULN)	Hold treatment (including MCS110) until resolved to ≤ Grade 1 or baseline. After recovery study treatment may be resumed per the investigator's discretion: chemotherapeutic agents reduced by 20% and MCS110 by 50%[b] of the previous dose.
	or	
	total bilirubin grade ≥ 2 with ALT grade ≥ 2	End treatment and discontinue patient from study.
Others (except for fatigue and alopecia)	Grade ≥ 3	*First episode:* reduce carboplatin and gemcitabine by 20% of original starting dose. *Second episode*: reduce both drugs by 40% of original starting dose.

[a]As soon as requirements for non-hematological toxicities are Grade ≤1 or baseline, study treatment should be delivered.
[b]Except for dose reductions of MCS110 dose of 2.5 mg/kg: in this case, the dose will be reduced to MCS110 1 mg/kg

6.2.2 Follow-up toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed up at least once every 7 days (or more frequently if required by institutional practices, or if clinically indicated) for 30 days, and subsequently at approximately 30 day intervals, until resolution or stabilization of the event, whichever comes first.

6.2.3 Anticipated risks and safety concerns

See Section 1.4.3 and Section 1.4.4.

6.3 Concomitant medications

6.3.1 Permitted concomitant therapy

In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed. The administration of bisphosphonates is permitted.

The patient must be told to notify the investigational site about any new medications, herbal remedies and dietary supplements he/she takes after the start of the study treatment. All medications (other than study treatment) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Prior and Concomitant Medications or the Surgical and Medical Procedures eCRF. Prior antineoplastic therapies including medications, radiotherapy, and surgery are to be recorded on the separate Prior Antineoplastic Therapy eCRF during

screening. Medication entries should be specific to trade name, dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

6.3.2 Permitted concomitant therapy requiring caution

Anticoagulation is permitted if the patients are already at stable doses of low molecular weight heparin (LMWH) for >2 weeks at time of first dose. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Concomitant treatment with warfarin sodium or any other coumarin-derivative anticoagulants should be cautioned due to potential drug interaction with carboplatin.

Since the renal effects of nephrotoxic compounds may be potentiated by carboplatin, drugs with nephrotoxicity should be used with caution. Aminoglycosides and phenytoin have been reported to have interaction with carboplatin and should be used with caution. Concomitant administration of carboplatin and phenytoin may cause decreased levels of serum phenytoin. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

Steroids used intermittently as anti-emetics are allowed but should be used with caution. Preferably, steroids should only be administered before chemotherapy treatment to minimize the use of steroids. The total dose per treatment cycle should not exceed 16 mg of dexamethasone or equivalent.

Statins should be used with caution since CK elevations are commonly seen.

6.3.3 Prohibited concomitant therapy

Any other anticancer or investigational treatment is not permitted while on study treatment. Additionally, other biologics (eg: antibodies and proteins) and immunosuppressive medication are not permitted while on this study.

Concomitant chronic corticosteroids (≥10 mg of prednisone or equivalent) are not allowed (See Section 5.3).

Treatment with hematopoietic colony-stimulating growth factors (e.g. G-CSF, may not be initiated unless the investigator deems it necessary. Hematopoetic colony-stimulating factors may counteract the effects of MCS110.

The use of live vaccines is not allowed through the whole duration of the study.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for pre-screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the Molecular pre-screening Informed Consent Form, the

patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface.

6.4.2 Treatment assignment and randomization

All eligible patients will be randomized in a 2:1 ratio to either Arm 1 (investigational arm): MCS110 + carbo/gem Or Arm 2 (control arm): carbo/gem. If there is no change in the MCS110 dose after the first early safety review meeting, the total number of patients for this study will be 78. If the dose is changed, the total number of patients for the study may be approximately-110, as the recruitment continues during the decision making.

The randomization will be done via Interactive Response Technology (IRT). The investigator or his/her delegate will contact the IRT after confirming that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the subject to a treatment arm. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff.

A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of treatment arms to randomization numbers.

6.5 Study drug preparation and dispensation

6.5.1 Study drug packaging and labeling

Study drug – MCS110

MCS110 is provided in a 10 ml glass vial each containing 150 mg MCS110 as a 20 mg/ml concentrate for solution for infusion.

Medication labels will be coded, printed in the local language, and will comply with local regulatory requirements. The storage conditions for study drug will be provided on the medication label.

Carboplatin/gemcitabine

Commercially available carboplatin and gemcitabine will be sourced locally by each study site. Generic carboplatin and gemcitabine may be used for study treatment.

6.5.2 Drug supply and storage

Study drug – MCS110

Please refer to the Pharmacy Manual for information regarding the MCS110 preparation and storage.

Carboplatin and gemcitabine

Carbo and gem should be stored and prepared according to the instructions on the package insert or summary of product characteristics of the commercial supply. The preparation (including all pre- and post-infusion anti-emetics medication) and disposal of carbo/gem must be in accordance with local institutional guidelines.

6.5.3 Study treatment compliance and accountability

6.5.3.1 Study treatment compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. Records of study medication used, dosages administered, and dosing period will be kept during the study.

All study medications will be administered to the patient by the study site staff. Compliance will be assured by administration of the study treatment under the supervision of Investigator or his/her designee.

6.5.3.2 Study treatment accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment (MCS110 and carbo/gem) according to local institutional drug accountability processes. Drug accountability will be noted by the field monitor during site visits and at the completion of the study.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability ledger to the Novartis address provided in the investigator folder at each site.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

No CRF will be used as a source document.

The table indicates which assessments produce data to be entered into the clinical database (D) or remain in source documents only (S) ("Category" column)

The pre-screening assessment and all screening assessments should be completed within 28 days before C1D1, except the pregnancy test which must be performed within 3 days before C1D1.

Assessments which are indicated to be performed at Screening/baseline and on Cycle 1 Day 1 need only to be repeated at Cycle 1 Day 1 if the Screening/baseline assessment was more than 3 days earlier.

Radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within 28 days of the first dose administered.

Table 7-1 Visit evaluation schedule

	Category	Protocol Section	Pre-Screening	Screening	Treatment period												End of Treatment	Follow-up phase		
					Cycle 1					Cycle 2		Subsequent cycles						30 day safety /(pregnancy) FU	60 day pregnancy FU	90 day safety /(pregnancy) FU
Day of cycle					1	2	4	8	15	1	8	1	2	4	8	15				
Mol. Pre-Screening ICF	D	7.1.1	x																	
Main ICF	D	7.1.2		x																
Patient history																				
Inclusion/exclusion criteria	D			x																
Medical History	D	7.1.2.2		x																
Demographics	D	7.1.2.2	x																	
Diagnose dates and stages for primary and advanced disease	D	7.1.2.2		x																
Prior antineoplastic	D	7.1.2.2		x																
Prior/concomitant medications and Non drug therapy	D	7.1.2.2		x	Continuously															
Randomization	D			x																
Physical examination	S	7.2.2.1		x	x					x		x					x			
Performance status	D	7.2.2.4		x	x					x		x					x			
Height	D	7.2.2.3		x																
Weight	D	7.2.2.3		x	x					x		x					x			
Vital signs	D	7.2.2.2		x	x	x	x	x	x	x	x	x[1]	x[1]	x[1]	x[1]	x[1]	x			
Hematology	D	7.2.2.5.1		x	x			x	x	x	x	x			x		x			
Chemistry	D	7.2.2.5.2		x	x			x	x	x	x	x			x[2]		x			
Thyroid Panel	D	7.2.2.5.5		x	Only if clinically significant according to the PI												x			

	Category	Protocol Section	Pre-Screening	Screening	Treatment period												Follow-up phase		
					Cycle 1					Cycle 2		Subsequent cycles					End of Treatment	30 day safety /(pregnancy) FU	60 day pregnancy FU	90 day safety /(pregnancy) FU
Day of cycle					1	2	4	8	15	1	8	1	2	4	8	15				
Coagulation	D	7.2.2.5.4		x	Only if clinically significant according to the PI												x			
Pregnancy test	D/S[4]	7.2.2.5.6		x[3]						x		x					x	X	X	X
Tumor evaluation as per RECIST v1.1 (CT chest/abdomen/pelvis + relevant)- MRI or PET/CT may be used instead of CT scans	D	7.2.1		x								At a minimum every 12 weeks (4 cycles)					x			
ECG	D	7.2.2.6.1		x	x[5]							Only C4D1[5] and C8D1[5]					x			
Adverse events	D	8.1.1	X[6]	Continuously														Continuously[8]		
Study drug/treatment administration	**D**	6.2																		
MCS110 administration	D	6.2.1			x			X[7]		x		x								
Carbo/gem administration	D	6.2.1			x			x		x	x	x			x					
Antineoplastic therapies since discontinuation of study treatment																		Continuously		

1: Vital signs for the subsequent cycles: to be performed on the days of dosing- if no dosing, to be performed when there is a PK time point
2: For the Chemistry at day 8 of the subsequent cycles, only the serum creatinine is mandated
3: Screening pregnancy test must be performed within 3 days before first dose administration
4: Category S for any safety FU pregnancy test. Monthly urine pregnancy tests must be performed for 90 days after the last dose of MCS110 or for 30 days after the last dose of carboplatin and gemcitabine or as recommended per the local approved labels for carboplatin and gemcitabine, whichever has the longest duration.
5: Only for patients receiving MCS110 in combination with carbo/gem
6: Pre-screening procedure related SAE's only
7: The MCS110 C1D8 dose may be omitted after a decision to change the regimen has been made at a safety review meeting
8: If a patient starts a new anticancer therapy during the safety follow-up, only AE's or SAE's suspected to be related to study treatment and associated concomitant medications will be collected from this time point.

7.1.1 Molecular pre-screening

Only patients whose tumors have a high TAM content per central assessment will be considered eligible for the study (Section 2.1 and Section 4.1).The assessment of TAM content will be obtained through submission of samples to a Novartis designated laboratory where IHC for CD163 (marker of TAM) will be performed. The central testing will be performed on newly obtained tumor samples (< 6 months old). Patients will be asked to sign and date an IRB/IEC approved "Molecular pre-screening informed consent form."

The pre-screening results from central testing for all patients (whether the patient is eligible or not for the study) will be communicated to the respective study center.

If confirmed that the patient's tumor has a high TAM content the patient may sign the study's main informed consent to begin screening procedures.

7.1.2 Screening

The study IRB/IEC approved ICF must be signed and dated prior to conducting any screening procedures that are not performed as part of the patient's standard of care.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. For details of assessments, refer to Table 7-1.

Screening assessments, must be repeated if performed outside of the specified screening windows. The pre-screening assessment and all screening assessments should be completed within 28 days before C1D1, except the pregnancy test which must be performed within 3 days before C1D1.

7.1.2.1 Information to be collected on screening failures

Subjects who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure. Both subjects who signed a molecular pre-screening ICF but are considered ineligible after molecular pre-screening, as well as subjects who are found not eligible after signing the main study consent will be considered as screening failures, and data will be handled in the same manner.

The molecular pre-screening failures or screening failures will be entered on the Screening Phase Disposition Page.

The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for Screen Failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a Serious Adverse Event during the Screening Phase (see Section 8 for SAE reporting details) or a SAE possibly related to a study procedure during the pre-molecular screening phase

7.1.2.2 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of tumor, details of prior anti-neoplastic treatments and any other assessments that are done for the purpose of determining eligibility for inclusion in the study. All medications and significant non-drug therapies (including

herbal medicines, physical therapy and blood transfusions) taken within 4 weeks prior to first dose of study drug must be recorded on the eCRF.

7.1.3 Treatment period

A treatment cycle is defined as 21 days. Please refer to Table 7-1 for details of the timing of required assessments and Section 7.1 for visit windows.

Patients will be treated until patient experiences unacceptable toxicity, progressive disease and/or treatment are discontinued at the discretion of the investigator or withdrawal of consent as described in Section 7.1.4 and Section 7.1.5.

Patients who discontinued 1 or 2 drugs in the Arm 1 regimen or 1 drug only in the Arm 2 regimen due to toxicity may continue with the remainder of drugs assigned at randomization upon discussion with the Novartis Medical Monitor.

Patients who have disease progression and have evidence of clinical benefit, such as disease shrinkage at other sites or symptomatic improvement, may continue study treatment upon documented discussion with the Novartis medical monitor.

For details of assessments, refer to Table 7-1.

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

The investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment may be discontinued if any of the following occur:

- Adverse event
- Lost to follow-up
- Disease progression
- Physician's decision
- Study terminated by the sponsor
- Subject/guardian decision
- Protocol deviation
- Technical problems

Study treatment will be discontinued if any of the following occur:

- Death
- Pregnancy

At the time patients discontinue study treatment, a visit should be scheduled as soon as possible, and within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study treatment, at which time all of the assessments listed for the EOT visit will be performed (Table 7-1). If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit rather than having the patient return for an additional visit. An End of Treatment Phase Disposition CRF page should be completed, giving the date and reason for stopping the study treatment. End of treatment/Premature withdrawal visit is not considered as the end of the study.

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.1.6. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.7.

7.1.4.1 Replacement policy

Patients will not be replaced.

7.1.5 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

Novartis will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow up.

7.1.6 Follow-up period

All patients must have safety evaluations 30 days and 90 days after the last dose of study treatment. It is up to the investigator to decide if the patient should come back to the clinic for the safety follow-up or if the follow-up can be performed via a telephone call. Information related to AEs (including concomitant medication taken for ongoing AEs) and ongoing anti-neoplastic treatments will be collected for 90 days after the last dose of study treatment (Table 7-1). Once a patient begins another anti-cancer therapy, only AE's and SAE's suspected to be related to the study treatment and the associated medications will be collected.

Antineoplastic therapies since discontinuation of study drug will be collected during the safety follow-up period.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow up should be recorded as such on the appropriate Disposition CRF.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor response will be determined locally according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Appendix 1). The local investigator's assessment will be used for the primary endpoint analysis and for treatment decision making.

Tumor evaluations will be performed at baseline within 28 days before start of treatment. All patients must undergo CT with i.v. contrast of the chest, abdomen, and pelvis. Radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within 28 days of the first dose administered.

If there are clinical signs of disease elsewhere, for example pain, palpable nodes etc., these areas should be evaluated with bone scan, bone X-ray, CT or MRI. PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast; however, MRI may be used to evaluate sites of disease where a CT without i.v. contrast is not adequate. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease.

Subsequent tumor evaluations will be performed at least every 12 weeks (4 cycles). Tumor evaluations will be performed at the EOT visit. If the last prior tumor evaluation was within 30 days of EOT or objective evidence of progressive disease has already been documented, then tumor evaluations do not need to be repeated at EOT. See Table 7-1 for details.

Tumor evaluations after the baseline assessment will include evaluation of all sites of disease identified at baseline, using the same technique that was used at baseline. If there was no evidence of disease in a body region outside of the chest, abdomen and pelvis at baseline, that region does not need to be imaged at subsequent assessments unless there is clinical concern for a new lesion in that body region.

All CRs and PRs MUST be confirmed by a second assessment not earlier than 28 days after the criteria for response are first met.

Table 7-2 Imaging collection plan

Procedure	Screening/ Baseline	During Treatment or Disease Progression FU
CT* with contrast enhancement (Chest, Abdomen, Pelvis)	Mandated	Mandated, at a minimum every 12 weeks (4 cycles), until disease progression. End of treatment.
Bone scan, bone x-ray, CT or MRI	If clinically indicated	Mandated (except bone scans, only per investigator's discretion) if findings at screening. At a minimum every 12 weeks (4 cycles) until disease progression. End of treatment.

*MRI or PET/CT may be used instead of CT scans, as described above.

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, weight, ECOG performance status, laboratory evaluations, 12-lead ECG in triplicate as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination must be performed according to the visit evaluation schedule in Table 7-1.

Assessments which are indicated to be performed at Screening/baseline and on Cycle 1 Day 1 need only to be repeated at Cycle 1 Day 1 if the Screening/baseline assessment was more than 3 days earlier.

The examination will include the examination of general appearance, skin, breasts, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. In addition, if indicated based on medical history and/or symptoms, rectal, external genitalia, and pelvic exams will be performed.

Physical examination will be performed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

Significant findings that were present prior to the signing of informed consent must be included in the Medical History page on the patient's CRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's CRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) will be assessed according to the visit evaluation schedule in Table 7-1.

Vital signs (body temperature, pulse rate, blood pressure) will be assessed pre-dose for Arm1 and Arm2. In addition for Arm1, blood pressure post-dose MCS110 (at the end of MCS110 infusion) will be assessed.

Blood pressure should be assessed after 5 minutes rest. The vital signs must be assessed in the same position during the study (either sitting or supine).

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.3 Height and weight

Height and body weight (in indoor clothing, but without shoes) will be measured according to the visit evaluation schedule in Table 7-1.

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-3 and according to the visit evaluation schedule in Table 7-1.

Table 7-3 ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

7.2.2.5 Laboratory evaluations

All laboratory parameters assessed for safety purposes will be evaluated locally, at the site.

Unscheduled assessment can be performed if clinically indicated.

Refer to Table 7-4 for a summary of the parameters to be evaluated according to Table 7-1

Table 7-4 Local Clinical Laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells (WBC) with Differential Count (Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Phosphate, Chloride, Creatinine, Sodium, Potassium, Creatine kinase (CK), Total Bilirubin, Urea or BUN, Uric Acid, Blood plasma Glucose (non-fasting) CK-MB baseline and Troponin (I or T) baseline If CK>5 x ULN: CK-MB (isoenzyme of CK), Troponin (I or T), If required to rule out myositis/rhabdomyolysis per local guidelines: Aldolase, Myoglobin
Tumor Markers	CA 15-3
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]
Thyroid	TSH- if abnormal take free T3 and T4
Urine	If required to rule out myositis/rhabdomyolysis per local guidelines: Myoglobin

7.2.2.5.1 Hematology

Please refer to Table 7-4 for a list of tests to be performed. For timing of assessments, refer to Table 7-1.

7.2.2.5.2 Clinical Chemistry

Please refer to Table 7-4 for a list of tests to be performed. For timing of assessments, refer to Table 7-1.

7.2.2.5.3 Tumor Markers

Please refer to Table 7-4 for a list of tests to be performed. For timing of assessments, refer to Table 7-1.

Following local IRB/EC approval of protocol amendment 6, tumor marker sample collection will no longer be required by the protocol.

7.2.2.5.4 Coagulation

Coagulation panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.5 Thyroid

Thyroid panel outlined in Table 7-4 will be performed as per the assessment schedule in Table 7-1.

7.2.2.5.6 Pregnancy

All females of childbearing potential will have a serum pregnancy test at screening within ≤ 3 days before first dose of study treatment. During the study, a serum pregnancy test should be done at day 1 of every cycle starting at Cycle 2, and at end of treatment.

If a patient becomes pregnant, study treatment should be discontinued immediately and the patient should be discontinued from the study. See Section 8.3 for pregnancy reporting.

During the safety follow-up, a urine pregnancy test must be performed 30, 60 and 90 days after stopping MCS110 for women of childbearing potential in Arm 1. Women of childbearing potential in Arm 2 will have a urine pregnancy test performed at least 30 days after stopping study treatment. For both arms, if the post-treatment contraception period for carboplatin and gemcitabine as per local approved label is longer than 30 days, monthly urine pregnancy tests must be performed until the end of the post-treatment contraception period. If the patient is not coming to the clinic for the follow-up visits, a pregnancy test should be performed at home or at a local doctor's office at each of the follow-up time points described above and the results will be communicated to the site staff. The follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

7.2.2.6 Cardiac Assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as per the assessment schedule in Table 7-1 and Table 7-5. Only screening and EoT ECGs are required in patients assigned to Arm 2. Blood samples scheduled at the same time point should be taken after the ECGs are completed. The ECGs on C1D1, C4D1 and C8D1 must be performed in triplicate.

Table 7-5 12 lead ECG collection plan

Cycle	Day	Time
Screening	-14 to -1	Anytime (all patients)
1	1	*Pre-dose (Arm 1 only)
1	1	*1h (±5 min) hour post end of MCS110 infusion (Arm 1 only)
4	1	*Pre-dose (Arm 1 only)
4	1	*1h (±5 min) hour post end of MCS110 infusion (Arm 1 only)
8	1	*Pre-dose (Arm 1 only)
8	1	*1h (±5 min) hour post end of MCS110 infusion (Arm 1 only)
EoT	-	Anytime (all patients)
Unscheduled**	-	Anytime (all patients)
* ECGs Performed in triplicate. **if on the same day as a PK sample, blood should be collected just after an ECG performed due to an unexpected cardiac signal.		

All ECGs (up to cycle 4 included) will be independently reviewed by a central laboratory. Instructions for the collection and transmission of ECGs to the central ECG laboratory will be provided in the ECG Manual.

ECGs at cycle 8 will be performed locally and recorded on a local ECG CRF page. After cycle 8, ECGs will be performed at the discretion of the investigator and will be recorded on a local ECG CRF page. These ECGs will not be reviewed by the central laboratory.

EoT ECG's are mandatory and will be reviewed locally.

Clinically significant abnormalities present at screening should be reported on the Medical History CRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page. All eligibility and patient management decisions should be made based on the local reading of the ECG.

7.2.3 Pharmacokinetics, pharmacodynamics (CSF-1) [redacted]

To assess PK, PD (CSF-1) [redacted] of MCS110, blood samples will be collected in Arm 1 to determine free MCS110 concentration in serum, total CSF-1 levels in plasma, [redacted]. To assess PK of carbo and gem, blood samples will be collected in both Arm 1 and Arm 2 to determine plasma concentrations of carbo, gem and 2',2'-difluoro-deoxyuridine (dFdU), the primary metabolite of gem.

7.2.3.1 Blood sample collection and handling

In Arm 1, for the first 15 patients, serial blood samples will be collected in Cycle 1 and 4, and pre-dose and sparse blood samples will be collected in Cycle 2, 3 and 5-8 (see details in Table 7-6). For subsequent patients, sparse blood samples will be collected (see details in Table 7-7). Note: If the MCS110 dose is reduced and/or the additional dose on C1D8 is omitted, the first 15 patients of the new dose regimen will be following the sampling schedule in Table 7-6, and the subsequent patients of the new dose regimen will follow the sampling schedule in Table 7-7.

In both Arm1 and 2, serial blood samples will also be collected in Cycle 1 and 4 (see details in Table 7-8).

All blood samples will be collected by either direct venipuncture or an indwelling cannula inserted in a forearm vein contra-lateral to the site of drug infusion to avoid potential loss of dose or contamination of blood samples. At each specified time-point, 2 mL blood sample will be collected for each analyte of MCS110, CSF-1 [redacted] (Table 7-6 to 7-7), and 1 mL blood sample will be collected for each analyte of carbo and gem (Table 7-8). Complete instructions for sample processing, handling and shipment will be provided in the [CMCS110Z2201 Laboratory Manual].

The exact date and clock times of study drug administration and blood sample collection will be recorded on the appropriate eCRF. Any sampling issues should be noted on the eCRF and on appropriate source documentation.

Following local IRB/EC approval of protocol amendment 6, pharmacokinetic sample collection for MCS110 will no longer be required by the protocol. In addition, CSF-1 [redacted] samples will no longer be collected.

Table 7-6 Pharmacokinetic (MCS110), CSF-1 [redacted] sample blood collection log (first 15 patients) in Arm 1 (not applicable after approval of protocol amendment 6)

Cycle	Day	Scheduled Time (Sampling window)[a]	Dose Reference ID (MCS110)[b]	PK Sample No (MCS110)[b]	CSF-1 Sample No[b]	[redacted]
1	1	Pre-dose (0 h)[d]	101	101	201	
1	1	1 h (± 5 min) post end of infusion	101	102	202	
1	2	24 h (± 2 h) post start of infusion	101	103	203	
1	4	72 h (± 6 h) post start of infusion	101	104	204	
1	8	Pre-C1D8 dose (0 h)[d] / 168 h post C1D1 dose	102/101[e]	105	205	
1	8[f]	1 h (± 5 min) post end of infusion of C1D8 dose	102	106	-	
1	15	168 h (±8 h) post start of infusion of C1D8 dose	102	107	206	
2	1	Pre-C2 dose (0 h)[d] / 336 h post C1D8 dose	103/102[e]	108	207	
3	1	Pre-C3 dose (0h)[d] / 504 h post C2 dose	104/103[e]	109	208	
4	1	Pre-C4 dose (0h)[d] / 504 h post C3 dose	105/104[e]	110	209	

Cycle	Day	Scheduled Time (Sampling window)[a]	Dose Reference ID (MCS110)[b]	PK Sample No (MCS110)[b]	CSF-1 Sample No[b]	[redacted]
4	1	1 h (± 5 min) post end of infusion of C4 dose	105	111	-	
4	2	24 h (± 2 h) post start of infusion of C4 dose	105	112	-	
4	4	72 h (± 6 h) post start of infusion of C4 dose	105	113	-	
4	8	168 h (± 8 h) post start of infusion of C4 dose	105	114	210	
4	15	336 h (±24 h) post start of infusion of C4 dose	105	115	211	
5	1	Pre-C5 dose (0 h)[d] / 504 h post C4 dose	106/105[e]	116	212	
6	1	Pre-C6 dose (0 h)[d] / 504 h post C5 dose	107/106[e]	117	213	
7	1	Pre-C7 dose (0 h)[d] / 504 h post C6 dose	108/107[e]	118	214	
8	1	Pre-C8 dose (0 h)[d] / 504 h post C7 dose	109/108[e]	119	215	
8	1	1 h (± 5 min) post end of infusion of C8 dose	109	120	-	
EOT			-	5000	6000	
Unscheduled [g]			-	1001+	2001+	

[a] Time relative to MCS110 dose. Blood samples (2 mL for each analyte) are to be collected from the arm contra-lateral to the infusion site.
[b] Dose reference ID and PK sample No. are for internal Novartis processes only.
[redacted]
[d] Pre-dose blood samples should be collected prior to start of MCS110 infusion.
[e] The first dose reference ID is for the first dose administered post the sample collection; the second dose reference ID is for the last dose administered prior to the sample collection.
[f] If the additional dose of MCS110 on C1D8 is omitted, the post-dose sample at C1D8 should be skipped.
[g] Unscheduled blood samples will be uniquely and sequentially numbered as 1001, 1002, etc. for MCS110 PK sample, and 2001, 2002, etc. for CSF-1 sample, and 3001, 3002, etc. for [redacted].

Table 7-7 Pharmacokinetic (MCS110), CSF-1 [redacted] sample blood collection log (subsequent patients) in Arm 1 (not applicable after approval of protocol amendment 6)

Cycle	Day	Scheduled Time (Sampling window)[a]	Dose Reference ID (MCS110)[b]	PK Sample No (MCS110)[b]	CSF-1 Sample No[b]	[redacted]
1	1	Pre-dose (0 h)[d]	101	101	201	
1	1	1 h (± 5 min) post end of infusion	101	102	202	
1	8	Pre-C1D8 dose (0 h)[d] / 168 h post C1D1 dose	102/101[e]	105	205	
1	8[f]	1 h (± 5 min) post end of infusion of C1D8 dose	102	106	-	
1	15	168 h (± 8 h) post start of infusion of C1D8 dose	102	107	206	
2	1	Pre-C2 dose (0 h)[d] / 336 h post C1D8 dose	103/102[e]	108	207	
3	1	Pre-C3 dose (0h)[d] / 504 h post C2	104/103[e]	109	208	

Cycle	Day	Scheduled Time (Sampling window)[a]	Dose Reference ID (MCS110)[b]	PK Sample No (MCS110)[b]	CSF-1 Sample No[b]	[redacted]
		dose				
4	1	Pre-C4 dose (0h)[d] / 504 h post C3 dose	105/104[e]	110	209	
4	1	1 h (± 5 min) post end of infusion of C4 dose	105	111	-	
4	8	168 h (± 8 h) post start of infusion of C4 dose	105	114	210	
4	15	336 h (±24 h) post start of infusion of C4 dose	105	115	211	
5	1	Pre-C5 dose (0 h)[d] / 504 h post C4 dose	106/105[e]	116	212	
6	1	Pre-C6 dose (0 h)[d] / 504 h post C5 dose	107/106[e]	117	213	
7	1	Pre-C7 dose (0 h)[d] / 504 h post C6 dose	108/107[e]	118	214	
8	1	Pre-C8 dose (0 h)[d] / 504 h post C7 dose	109/108[e]	119	215	
8	1	1 h (± 5 min) post end of infusion of C8 dose	109	120	-	
EOT			-	5000	6000	
Unscheduled [g]			-	1001+	2001+	

[a] Time relative to MCS110 dose. Blood samples (2 mL for each analyte) are to be collected from the arm contra-lateral to the infusion site.
[b] Dose reference ID and PK sample No. are for internal Novartis processes only.
[redacted]
[d] Pre-dose blood samples should be collected prior to start of MCS110 infusion.
[e] The first dose reference ID is for the first dose administered post the sample collection; the second dose reference ID is for the last dose administered prior to the sample collection.
[f] If the additional dose of MCS110 on C1D8 is omitted, the post-dose sample at C1D8 should be skipped.
[g] Unscheduled blood samples will be uniquely and sequentially numbered as 1001, 1002, etc. for MCS110 PK sample, and 2001, 2002, etc. for CSF-1 sample, and 3001, 3002, etc. for [redacted].

Following local IRB/EC approval of protocol amendment 6, pharmacokinetic sample collection for carbo/gem will no longer be required by the protocol.

Table 7-8 Pharmacokinetic (carbo/gem) sample blood collection log in both Arm 1 and Arm 2 (not applicable after approval of protocol amendment 6)

Cycle	Day	Scheduled Time (Sampling window)[a]	Dose Reference ID (gem)[b]	PK Sample No (gem)[b]	Dose Reference ID (carbo)[b]	PK Sample No (carbo)[b]
1	1	Pre-dose (0h)[c]	201	401	301	501
1	1	End of Gem infusion (± 5 min)	201	402	-	-
1	1	End of Carb infusion (± 5 min)	201	403	301	502
1	1	2 h (± 10 min) post start of infusion of gem dose	201	404	301	503
1	1	3 h (± 10 min) post start of infusion of gem dose	201	405	301	504
1	1	5 h (± 30 min) post start of infusion of gem dose	201	406	301	505
1	2	24 h (± 2 h) post start of infusion of	201	407	301	506

Cycle	Day	Scheduled Time (Sampling window)[a]	Dose Reference ID (gem)[b]	PK Sample No (gem)[b]	Dose Reference ID (carbo)[b]	PK Sample No (carbo)[b]
		gem dose				
4	1	Pre-dose (0h)[c]	202	408	302	507
4	1	End of C4D1 gem infusion (± 5 min)	202	409	-	-
4	1	End of C4D1 carb infusion (± 5 min)	202	410	302	508
4	1	2 h (± 10 min) post start of infusion of C4D1 gem dose	202	411	302	509
4	1	3 h (± 10 min) post start of infusion of C4D1 gem dose	202	412	302	510
4	1	5 h (± 30 min) post start of infusion of C4D1 gem dose	202	413	302	511
4	2	24 h (± 2 h) post start of infusion of C4D1 gem dose	202	414	302	512

[a] Blood samples (1 mL for gem and 1 mL for carbo) are to be collected from the arm contra-lateral to the infusion site.
[b] Dose reference ID and PK sample No. are for internal Novartis processes only.
[c] Pre-dose blood sample should be collected prior to start of gem infusion for gem PK sample, and prior to start of carbo infusion for carbo PK sample, respectively.

7.2.3.2 Analytical methods

Free MCS110

Free MCS110 (unbound drug) will be determined in serum by a validated Enzyme Linked Immunosorbent Assay (ELISA) with a lower limit of quantification (LLOQ) at 20 ng/mL and an upper limit of quantification (ULOQ) at1000 ng/mL. The ELISA method uses CSF-1 as the capture reagent and an anti-human IgG conjugate as the detection reagent. The detailed method descriptions of the free MCS110 assay will be included in the corresponding bioanalytical data report.

Total CSF-1

Total CSF-1 will be determined in plasma (K2 EDTA) by a validated Enzyme Linked ImmunoSorbent Assay (ELISA) with an anticipated LLOQ at 1.5 ng/mL and an ULOQ at 48 ng/mL.

The ELISA method uses a goat anti-human CSF-1 antibody as the capture reagent and a rabbit anti-human CSF-1 and a goat anti-rabbit conjugate as the detection reagents. The detailed method descriptions of the total CSF-1 assays will be included in the corresponding bioanalytical data report.

Carbo

Plasma (K2 EDTA) concentration of carboplatin will be determined by a validated assay using ultra-filtration and analysis of the filtrate by liquid chromatography - tandem mass spectrometry (LC-MS/MS) with an anticipated LLOQ at 2 ng/mL using 50 µL of plasma. The detailed method descriptions of the carboplatin assay will be included in the corresponding bioanalytical data report.

Gem and dFdU

Plasma (Lithium Heparin) concentration of gem and dFdU (the primary metabolite) will be determined by a validated concomitant assay using protein precipitation and analysis of reconstituted sample by LC-MS/MS with anticipated LLOQs at 0.5 ng/mL for gemcitabine and 5 ng/mL for dFdU using 50 µL of plasma. The detailed method descriptions of the gem and dFdU assay will be included in the corresponding bioanalytical data report.

7.2.4 Biomarkers

Following local IRB/EC approval of protocol amendment 6, biomarker sample collections will no longer be required by the protocol.

As outlined in Table 7-9, biomarker analyses will be used to investigate the effect of MCS110 at the molecular and cellular level to determine how baseline biomarker status and/or changes from baseline values may relate to exposure, clinical outcome, and/or resistance mechanisms.

The concept for this study is that induction of an immune response to chemotherapy may lead to enhanced tumor responses. MCS110 is an antibody directed towards CSF-1 which suppresses the development and survival of TAMs. Moreover, several studies have shown that TAM depletion leads to induction of an immune response by activation of CD8+ T-cells (DeNardo 2011, Ries 2014). Only patients with a high content of TAMs (CD163+), the target cell for MCS110, in their tumor tissue will be eligible for participation in this study.

Clinical studies have shown that chemotherapy response is higher in patients whose tumors have high TIL content (von Minckwietz 2014). Additionally, it has been shown in preclinical models that a basic level of TILs is needed to get an additional effect of TAM depletion regarding immunogenic response and enhanced chemotherapy response (Ruffell, 2014). Thus, TIL counts as determined by CD8 protein expression will also be examined in pre and post-dose tumor samples.

All biopsies in Table 7-9 are mandatory and must be obtained, if medically feasible.

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample collection analysis may be omitted at the discretion of Novartis.

The sample collection information must be entered on the appropriate sample collection log eCRF page(s) and requisition form(s). Detailed instructions for the collection, handling, and shipment of tumor samples are outlined in the laboratory manual for the study.

Table 7-9 Biomarker sample collection plan (not applicable after approval of protocol amendment 6)

Sample Type	Visit/Time point	Volume	Marker	Purpose
Tumor samples				
Newly obtained tumor sample (mandatory) (Tumor biopsy sample to be considered "newly obtained" if <6 months old)	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
Newly obtained tumor sample (Tumor biopsy sample to be considered "newly obtained" if <6 months old)	Screening * (mandatory) Between C2D8 and C3D1** (mandatory, if medically feasible)	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]
[redacted]				
Blood samples				

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

[redacted]

* Using remaining tissue from newly obtained pre-screening tumor biopsy
**All biopsies must be conducted by a professional with expertise in the procedure. 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 investigators 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]

7.2.4.1 Tumor and blood samples

[redacted]

7.2.4.1.2 Potential pharmacodynamic markers

Depending upon tumor sample availability from newly obtained screening and interim tumor biopsies, these samples will be used to assess TIL counts by CD8 IHC as well as other immune-signature related biomarkers. Further, contingent upon the availability of enough

material, additional broad genetic profiling of baseline samples will also be conducted to evaluate any genetic correlations with response to therapy

Potential changes in serum biomarkers will also be explored to look for correlations with response to therapy in both pre-dose and post-dose samples (see Table 7-9). Serum CTX-I will be evaluated as a marker of bone resorption. [redacted] Additional markers or methods may be utilized if indicated by new findings from the literature as well as from Novartis internal data.

7.2.4.2 Other Biomarkers

If the patient agrees, any remaining samples (tumor and/or blood) may be stored for up to 15 years and further analyzed to address scientific questions related to the study treatment and/or cancer. This research may also help to develop ways to detect, monitor and/or treat cancer. The decision to perform such exploratory biomarker research studies would be based on outcome data from this study and from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained.

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. For the pre-screening informed consent, only pre-screening procedure related SAE's will be reported in the CRF.

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 90 days following the last dose of study treatment regardless of suspected causality. Once a patient begins another anti-cancer therapy, only AE's suspected to be related to the study treatment and associated concomitant medications should be reported at least for 90 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study but is collected as a seriousness criteria; rather, information about deaths will be collected though a Death form.

The occurrence of adverse events should be sought by non-directive questioning of the patient (subject) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (subject) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1 and which seriousness criteria have been met

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

8.1.2 Laboratory abnormalities

8.1.2.1 Definition and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or

require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.2 Serious adverse events

8.2.1 Definitions

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event.

Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some patients. In this situation, progression is evident in the patient's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

8.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 90 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 90 days period or once a patient begins another anti-cancer treatment should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signatures are to be found in the investigator folder provided to each site.

Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Chief Medical Office and Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Furthermore, any pregnancies occurring after discontinuation of study treatment (up to 90 days or during the post treatment contraception period as recommended per the local approved labels, whichever has the longest duration) must be reported to Novartis within 24 hours of learning of its occurrence.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Chief Medical Office and Patient Safety (CMO&PS).

Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

8.4 Warnings and precautions

No evidence available at the time of the approval of this study protocol indicated that special warnings or precautions were appropriate, other than those noted in the provided Investigator Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.5 Steering Committee

During the safety review(s), safety profiles of all the patients who receive treatment in the study will be reviewed. The detailed procedure of the safety review meetings are specified in Section 4.1. 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 (see Section 10.7) at the respective time.

A Steering Committee constituted of members of the Novartis Translational Clinical Oncology Leadership Team will be formed for this study. If the monitoring of the study data requires a decision to be taken on the continuation of the study, then the relevant data (e.g., safety data or primary analysis and predictive probability of success (PPOS)) will be communicated to the Steering Committee for decision making purposes.

9 Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

PK samples drawn during the course of the study will be collected by investigational sites and analyzed by Novartis delegated central Laboratory.

Biomarker samples drawn during the course of the study will be collected by investigational sites and analyzed by a Novartis-designated laboratory.

All ECGs (up to cycle 4 included) collected per assessment schedule Table 7-5 will be independently reviewed by a central laboratory. Cycle 8 (only for patients in Arm 1) and EoT ECG's will be reviewed locally. After cycle 8, ECGs will be performed at the discretion of the investigator, reported on a local ECG CRF page and not be reviewed centrally.

Radiological assessments obtained for patients enrolled on study may be centrally collected by an imaging CRO designated by Novartis and may be assessed centrally in addition to the local assessment if deemed necessary. The investigator's staff will be instructed on how to send data from these radiological assessments to a CRO for central review when needed.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Dictionary, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

PK, biomarker samples and ECG data (only until cycle 4 for ECG) will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

For EDC studies, after database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Randomization codes will be tracked using an Interactive Response Technology. The system will be supplied by a vendor.

10 Statistical methods and data analysis

The data will be analyzed by Novartis.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, and all relevant pharmacokinetic and pharmacodynamic measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data). In all cases, data will be analyzed and/or presented separately for each study arm and treatment group.

The analysis of study data for the clinical study report (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.

10.1 Analysis sets

10.1.1 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.

10.1.2 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.

10.1.3 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS who have an adequate tumor assessment at baseline, a follow-up tumor assessment ≥6 weeks after starting treatment (unless disease progression is observed before that time), and no major protocol deviations.

All major protocol deviations leading to exclusion from the PPS will be detailed in the Reporting and Analysis Plan (RAP).

The PPS will define the patients used in the sensitivity analysis of the primary endpoint.

If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.1.4 Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who have evaluable pharmacokinetic (PK) data. The PAS will be used for summaries of PK concentration data, PK parameters [redacted]. 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.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively by study arm and treatment group.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

Duration of exposure to study treatment in cycles, as well as actual total doses, actual dose intensities, and relative dose intensities of all study drugs will be summarized using descriptive statistics by study arm and treatment group for the safety set.

10.3.2 Concomitant medications

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized by study arm and treatment group for the safety set by ATC (Anatomical therapeutic chemical classification system) term.

10.3.3 Compliance

Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and

summarized by study arm and treatment group. Compliance to the study treatment within each study arm 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.

10.4 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. For simplicity, throughout this section, the MCS110+carbo/gem arm will be used to refer to patients randomized to Arm 1 at the MCS110 final confirmed dose.

10.4.1 Variable

The primary efficacy endpoint is progression free survival (PFS) based on local Investigator assessment, as defined in RECIST 1.1. The hazard ratio (HR) for PFS between the MCS110+ carbo/gem arm and the carbo/gem arm will be estimated. Note: if blinded central review is performed, then analyses specified for all efficacy endpoints based on local assessments will be additionally performed on the response evaluations from the blinded review.

10.4.2 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.

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

In addition, estimated HR for the MCS110 + carboplatin/gemcitabine arm compared to the carboplatin/gemcitabine arm along with the one-sided 90% credible interval will be produced. Moreover, Kaplan-Meier plots will be adopted in order to present PFS graphical outputs for both the MCS110 + carboplatin/gemcitabine arm and the carboplatin/gemcitabine arm.

10.4.3 Handling of missing values/censoring/discontinuations

If a patient has not had an event, PFS is censored at the date of last adequate tumor assessment, as defined in the in the RECIST 1.1 (Appendix 1). Patients for whom no best overall response can be assessed at the time of the primary analysis will be treated as treatment failures in the analysis of ORR. The reason for discontinuation from study will be

summarized and listed, along with dates of first and last study drug treatment, duration of exposure to study drug treatment and date of discontinuation for each patient.

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

10.4.4 Supportive analyses

The PPS will be used in a supportive analysis of the primary endpoint.

[redacted] supportive analyses will be conducted if appropriate and defined in the RAP.

10.5 Secondary objectives

10.5.1 Other secondary efficacy objectives

Response: Individual lesion measurements will be listed along with the overall lesion response and Best Overall response. ORR and CBR will be summarized by study arm and treatment group with accompanying 95% confidence intervals.

DOR: DOR will be presented descriptively using Kaplan Meier plots by treatment group. In addition, the median DOR and corresponding 95% confidence interval will be presented.

10.5.2 Safety objectives

10.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by study arm and treatment group.

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

- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to 90 days after last dose of study medication
- post-treatment period: starting at day 91 after last dose of study medication.

10.5.2.2 Adverse events (AEs)

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

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by study arm and treatment group.

Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and study arm and treatment group.

10.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology and biochemistry laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges

In addition to the above mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

10.5.2.4 Other safety data

ECG

- shift table baseline to worst on-treatment result for overall assessments
- listing of ECG evaluations for all patients with at least one abnormality.

Vital signs

Definitions of notably abnormal results have to part of the CDP, MAP, CSP and RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

10.5.2.5 Supportive analyses for secondary objectives

Any supportive analyses that are considered appropriate for secondary variables will be described in the RAP prior to DBL.

10.5.2.6 Tolerability

Tolerability of study drug treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruption and dose reductions will be listed by patient and summarized.

10.5.3 Pharmacokinetics

All subjects who have evaluable PK data will be included in the PK data analysis. PK parameters will be determined using non-compartmental method(s) for MCS110, carboplatin, gemcitabine, and dFdU (the primary metabolite of gemcitabine). PK parameters such as those listed in Table 10-1 will be estimated and reported, when applicable. [redacted]

Table 10-1 Non-compartmental pharmacokinetic parameters

AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume^{-1})
AUCinf	The AUC from time zero to infinity (mass x time x volume^{-1})
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume^{-1})
Cmax	The maximum (peak) observed serum/plasma drug concentration after single dose administration (mass x volume^{-1})
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
T1/2	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CL	The total body clearance of drug from the serum/plasma (volume x time^{-1})
Vz	The volume of distribution during terminal phase (associated with λz) (volume)

10.5.3.1 Data handling principles

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) will be handled as zero in summary statistics, and reported as is in data listings. Any missing pharmacokinetic parameter data will not be imputed.

10.5.3.1.1 Basic Tables, Figures and Listings

Descriptive statistics (mean, standard deviation, CV% or median (range)) will be presented for all parameters by analyte, study arm and treatment group 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 is generally evaluated by a nonparametric method, median values and ranges will be presented for this parameter. [redacted]

Descriptive graphical plots of individual and mean serum/plasma concentration versus time profiles of MCS110, CSF-1 and other PD biomarkers (e.g. CTX-1, and monocytes) will be generated. Further graphical exploratory analyses will be carried out if deemed appropriate.

[redacted]

[redacted]

10.5.4 Biomarkers

10.5.4.1 Outline of the data analysis

As a project standard, the data collected from tumor samples in the clinical database will be analyzed by a Novartis designated laboratory and Novartis Oncology study team. [redacted]

If the number of samples is inadequate to perform a rigorous data analysis, then only the available data will be listed. Additional analyses that may be performed after the completion of the end-of-study clinical study report 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. Any additional data analysis will be described in an addendum of the RAP or in a stand-alone analysis plan document, as appropriate.

10.5.4.2 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.

10.5.4.3 Data analysis principles

10.5.4.3.1 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.

10.5.4.3.2 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 of the H-scores. The H-score data will also be listed by patient for all these markers. Besides, the TAM and TIL content in primary archival tissue and the pre-treatment biopsy will also be compared and presented in the similar way. 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.

10.5.4.3.3 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.

[redacted]

10.7 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 (Section 2.2 and Section 4.1). If the dosing regimen is changed after the first safety review meeting, an additional safety review for this new treatment regimen will take place after 9 patients have been randomized and completed two cycles of either MCS110 (at the new dosing regimen) + carbo/gem or carbo/gem alone, or discontinued earlier due to adverse events. Any subsequent MCS110 changes of the dosing regimen will be followed by an additional safety review(s) after 9 patients have been randomized and completed two cycles of either MCS110 (at the new dosing regimen) + carbo/gem or carbo/gem alone, or discontinued earlier due to adverse events.

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 (Section 8.5).

Outputs to be produced for the safety review will be identified in the RAP.

Efficacy and safety data will be reviewed on a regular basis as mentioned in 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 for efficacy will be taken following the review of this

data. (Note: early stopping may be recommended by the Steering Committee for safety or futility purposes.)

Analyses produced for this review will include but may not be limited to:

- Analysis of primary efficacy endpoint
- 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
- Summaries of key baseline characteristics Outputs to be produced for monitoring will be identified in the RAP.

10.8 Sample size calculation

For this trial, information currently available coming from O'Shaughnessy 2011 for carboplatin/gemcitabine (see 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 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 10-2.

Table 10-2 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.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

Novartis will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

Additional consent form *(if applicable)*

Sub-studies and studies with an optional Exploratory Biomarker component will have a separate consent form covering those studies. This form will be adapted for each Study based on a standard template used globally for all Studies. These informed consent forms will be submitted for ethical approval together with the Study Protocol and the main informed consent form of the Study. If a subject opts not to participate in the optional assessments, this in no way affects the subject's ability to participate in the main research study.

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.3.

11.5 Publication of study protocol and results

Novartis is committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results , whatever their outcome.

Novartis assures that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov, before study start. In addition, results of interventional clinical trials in adult patients are posted on www.novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion (i.e.,LPLV), , those for interventional clinical trials involving pediatric patints within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted.

Authors will not receive remuneration for their writing of a publication, either directly from Novartis or through the professional medical writing agency. Author(s) may be requested to present poster or oral presentation at scientific congress; however, there will be no honorarium provided for such presentations.

As part of its commitment to full transparency in publications, Novartis supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

For the Novartis Guidelines for the Publication of Results from Novartis-sponsored Research, please refer to www.novartis.com.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or

evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available to inspections by Novartis or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must

be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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14 Appendices

14.1 Appendix 1: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival and Overall Survival (based on RECIST 1.1)

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Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression
UNK	Unknown

14.1.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 14.1.2 and the definition of best response in Section 14.1.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.18 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.1.28 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

14.1.3 Definitions

14.1.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 14.1.26.

Measurable lesions (both nodal and non-nodal)

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components, that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.
- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at

baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

- **Cystic lesions**:
  - Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
  - 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

14.1.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.1.26.

14.1.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will

be accepted for follow up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound**: When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.1.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.1.4.
- **Nodal target**: See Section 14.1.4.

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

14.1.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-1) and non-target lesions (Table 14-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-3) as well as the presence or absence of new lesions.

14.1.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore all such data applicable to a particular visit should be associated with the same assessment number.

14.1.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

14.1.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

14.1.12 Determination of target lesion response

Table 14-1 Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm^2.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

[1]. SOD for CR may not be zero when nodal lesions are part of target lesions
[2]. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3]. Methodology change See Section 14.1.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-1 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
    - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
    - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
    - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

14.1.13 Determination of non-target lesion response

Table 14-2 Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.1.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.1.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.1.6.

14.1.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-3.

Table 14-3 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1]. This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2]. Once confirmed PR was achieved, all these assessments are considered PR.
[3]. As defined in Section 14.1.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be 'unknown' unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

14.1.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.26 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- -For non-randomized trials where response is the primary endpoint, confirmation is needed.
- -For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response 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 where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ 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 early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Objective response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD.

Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

14.1.18 Time to event variables

The protocol should state which of the following variables is used in that study.

14.1.19 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

14.1.20 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

14.1.21 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

14.1.22 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

14.1.23 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988)

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

14.1.24 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.1.23. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

14.1.25 Definition of start and end dates for time to event variables

Assessment date

For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates

For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.

For the calculation of duration of response the following start date should be used:

- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates

The end dates which are used to calculate 'time to event' variables are defined as follows:

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.1.26).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

14.1.26 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-4.

Table 14-4 Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 14.1.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only non-measurable disease.

14.1.27 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and RAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 14.1.25, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005) as a reference, the following analyses can be considered:

Table 14-5 Options for event dates used in PFS, TTP, duration of response

Situation		Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or RAP	Outcome
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy (4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 14.1.25
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25.
[3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses

Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 14-5 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or RAP documentation.

14.1.28 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

14.1.29 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or RAP documentation. Any deviations from protocol must be discussed and defined at the latest in the RAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the RAP documentation before database lock).

14.1.30 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to follow-up, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:

- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

14.1.31 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:

- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision

- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

14.1.32 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

14.1.33 Programming rules

The following should be used for programming of efficacy results:

14.1.34 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

14.1.35 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.1.25). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

14.1.36 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

14.1.37 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

14.1.38 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

14.1.39 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.1.25. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anti-cancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

14.1.40 References (available upon request)

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Ellis S, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials 2008; 29: 456-465

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