NOVARTIS

Clinical Development

MCS110

Protocol CMCS110Z2102 / NCT02807844

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

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List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BLRM	Bayesian Logistic Regression Model
CBR	Clinical Benefit Rate
CDP	Clinical Development Plan
cfDNA	Circulating free DNA
CK	Creatine Kinase
CL	Clearance
Cmax	maximum drug concentration
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSF-1	Colony Stimulating Factor 1 (see M-CSF)
CSF-1R	Colony Stimulating Factor 1 Receptor
CSR	Clinical study report
CTLA-4	Cytotoxic T-Lymphocyte-Associated protein 4
CTX-1	C-terminal Telopeptide of type I collagen
CYPP450	Cytochrome P450
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOT	End Of Treatment
eSAE	Electronic Serious Adverse Event
ESMO	European Society for Medical Oncology
EWOC	Escalation With Overdose Control
FIH	First In Human
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HNSTD	Highest No Severely Toxic Dose
HV	Healthy Volunteer
i.v.	intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IG	Immunogenicity
IL-2	Interleukin 2
IRB	Institutional Review Board
irRC	Immune-related Response Criteria
K_d	Constant of dissociation
LDH	Lactate Dehydrogenase
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
MDSCs	Myeloid-Derived Suppressor Cells
MRT	Mean Residence Time
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
o.d.	*omnia die*/once a day
ORR	Overall Response Rate
OS	Overall Survival
p.o.	*per os*/by mouth/orally
PD	Pharmacodynamic / Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression Free Survival
PgP	P-glycoprotein 1 also known as multidrug resistance protein 1
PHI	Protected Health Information
PR	Partial Response
PVNS	Pigmented VilloNodular Synovitis
Q2W, Q3W, Q4W	Respectively, every two, three, four week
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
RP2D	Recommended Phase two Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEB	Staphylococcal Enterotoxin B
SOP	Standard Operating Procedure
TAM	Tumor Associated Macrophage
TCP	thrombocytopenia
Tregs	Regulatory T cells

Glossary of terms

Assessment	A procedure used to generate data required by the study
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
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.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological sample
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 timepoints
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary:

Protocol number	CMCS110Z2102
Title	A Phase Ib/II, open label, multicenter study of MCS110 in combination with PDR001 in patients with advanced malignancies
Brief title	Phase Ib/II study of MCS110 in combination with PDR001 in patients with advanced malignancies
Sponsor and Clinical Phase	Novartis Ib/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study of MCS110 with PDR001 is to characterize the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of the combination of MCS110 with PDR001 in adult patients with solid tumors Combined treatment with MCS110 and PDR001 is expected to result in TAM depletion, enhanced T-cell activation and synergistic antitumor activity in the clinical setting.
Primary Objectives	• **Phase Ib**:To characterize the safety and tolerability of MCS110 in combination with PDR001 in patients with advanced solid malignancies and to identify a recommended dose combination for Phase II • **Phase II**: To estimate the anti-tumor activity of the combination of MCS110 with PDR001
Secondary Objectives	• To further characterize the safety and tolerability of MCS110 given in combination with PDR001 • To characterize the pharmacokinetic profile of the combination of MCS110 with PDR001 • To further evaluate the preliminary anti-tumor activity of the combination of MCS110 with PDR001 by additional efficacy measures • To assess emergence of anti-MCS110 or anti-PDR001 antibodies • [redacted] • To describe survival with MCS110 and PDR001 given in combination
Study design	• This study has been designed as a Phase Ib/II, multi-center, open-label study starting with a Phase Ib dose escalation part followed by a Phase II part. • MCS110 and PDR001 will be administered every 3 weeks until patient experiences unacceptable toxicity, progressive disease per immune related Response Criteria (irRC) and/or treatment is discontinued at the discretion of the investigator or the patient.
Population	The **Phase Ib** part of the study will be conducted in adult patients with advanced melanoma, endometrial, pancreatic and triple negative breast cancer. The **Phase II** part of the study will be conducted in adult patients enrolled in distinct groups: • PD1/PD-L1 treatment naïve TNBC • PD1/PD-L1 treatment naïve pancreatic cancer • PD1/PD-L1 treatment naïve endometrial carcinoma • PD1/PD-L1 treatment resistant melanoma.

Inclusion criteria	• Age ≥ 18 years [For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]
	• **Phase Ib part**: Patients with advanced melanoma, endometrial carcinoma, pancreatic or triple negative breast cancer, with measurable or non-measurable disease as determined by RECIST version 1.1, who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists.
	• **Phase II part**: Patients with advanced solid tumors with at least one measurable lesion as determined by RECIST version 1.1, who have received standard therapy or are intolerant of standard therapy, who have progressed following their last prior therapy, and fit into one of the following groups:
	  • Group 1: TNBC who did not receive prior anti-PD-1/PD-L1 treatment
	  • Group 2: Pancreatic adenocarcinoma who did not receive prior anti-PD-1/PD-L1 treatment
	  • Group 3: Endometrial carcinoma who did not receive prior anti-PD-1/PD-L1 treatment
	  • Group 4: Melanoma who progressed on prior PD-1- and PD-L1-directed therapies.
	• ECOG Performance Status ≤ 2.
	• Patient must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patient must be willing to undergo a new tumor biopsy at screening, and during therapy on this study. Exceptions for patients with sites of disease not amenable to biopsy may be considered after discussion with the sponsor.

Exclusion criteria	• Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy
	• History of severe hypersensitivity reactions to other mAbs
	• Patient having out of range laboratory values defined as:
	  • Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min
	  • Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
	  • Alanine aminotransferase (ALT) > 3 x ULN
	  • Aspartate aminotransferase (AST) > 3 x ULN
	  • Absolute neutrophil count < 1.0 x 10^9/L
	  • Platelet count < 100 x 10^9/L
	  • Hemoglobin (Hgb) < 9 g/dL
	• Impaired cardiac function or clinically significant cardiac disease
	• Active autoimmune disease or a documented history of autoimmune disease within three years before screening
	• Active infection, including active tuberculosis, requiring systemic antibiotic therapy
	• Known history of HIV infection
	• Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or requiring antiviral treatment
	• Malignant disease, other than that being treated in this study
	• Any medical condition that would prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results, including but not limited to:
	  • Prior immune-related adverse events requiring treatment discontinuation
	  • Ongoing symptomatic interstitial lung disease (ILD), noninfectious pneumonitis or history of drug induced interstitial lung disease

	• Systemic anti-cancer therapy within 2 weeks or 5 x T ½, whichever is longer of the first dose of study treatment. Cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, within 4 weeks and CTLA-4, PD-1 or PD-L1 antagonists, within 6 weeks of the first dose of study treatment • Patients requiring chronic treatment with systemic steroid therapy or any immunosuppressive therapy • Use of any live vaccines against infectious diseases within 4 weeks of initiation of study treatment • Major surgery within 2 weeks of the first study drug • Radiotherapy within 2 weeks of the first dose of study drug • Participation in an interventional, investigational study within 2 weeks of the first dose of study treatment • Presence of ≥ CTCAE Grade 2 toxicity • Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF) ≤ 2 weeks prior start or study drug. • Pregnant or lactating women • Women of child-bearing potential, unless they are using highly effective methods of contraception
Investigational and reference therapy	MCS110 and PDR001
Efficacy assessments	Tumor assessment per RECIST v1.1 and per irRC
Safety assessments	Incidence and severity of AEs and SAEs, including changes in laboratory values, vital signs and ECGs
Other assessments	• Serum PK parameters and immunogenicity • [redacted]
Data analysis	The study data will be analyzed and reported based on all patients' data of the Phase Ib and Phase II parts up to the time when all patients have completed at least six cycles of treatment or discontinued the study.
Key words	Phase Ib/II, MCS110, PDR001, immune checkpoint inhibitor, PD-1, PD-L1, CSF-1, tumor associated macrophage.

Amendment 05 (23-Jul-2019)

Amendment rationale

This protocol amendment revises the definition of end of study to include the option for patients still on study treatment and who, in the opinion of the investigator, are still deriving clinical benefit at the time of end of study, to transfer to another study to continue providing study treatment to these patients or to an alternative treatment option.

In addition, based on a health authority request, the use of condoms for male study participants and pregnancy outcome collection for female partners of male study participants has been reintroduced only for patients treated in Korea. Exclusion criterion #21 has been updated accordingly.

Lastly, PK and IG assessments are no longer mandated at the End of Treatment visit as sufficient data have already been collected.

Study Status

The CMCS110Z2102 study started enrollment on 29-Jun-2016. The last patient was enrolled on 10-Jan-2019. The pre-defined decision criteria for further expansion of the pancreatic cancer, TNBC, endometrial cancer and melanoma groups were not met (see Section 4.2 and 10.4.4.2). By consequence, no further patients will be enrolled in this study. A total of 141 patients have been treated: 60 patients in the dose escalation part and 81 patients in Phase II part of study (20 in pancreatic group, 20 in TNBC group, 21 in endometrial group and 20 in melanoma group). As of 08-Jul-2019, 6 patients were still on treatment (in phase II only) and 41 patients in survival follow-up.

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 underline for insertions.

Section 4.3: Definition of end of study:

- Addition of language to account for patients who would transfer into another study or an alternative treatment option to continue provision of study treatment.

Section 5.3: Exclusion criteria:

- Re-insertion of exclusion criteria 21 for Korea only where the use of condom for male study participants remains mandatory.

Section 7.1.3: Discontinuation of study treatment:

- Addition of language to specify that patients who transfer to another study or an alternative treatment option to continue provision of study treatment will complete end of treatment procedures.

Section 7.1.5: Follow up period:

- Addition of language to specify that patients who transfer into another study or an alternative treatment option to continue provision of study treatment will not complete the

safety, disease progression and survival follow up. For all other patients, the safety evaluation period will be completed but the disease-progression and survival follow up will not be performed or pursued.

Section 7.2.3: Pharmacokinetics and immunogenicity assessments, Table 7-1: Visit evaluation schedule and Table 7-7: Phase II Part: Pharmacokinetic blood collection log for MCS110, PDR001 and IG samples:

- Removal of PK and IG samples collection at End of Treatment.

Section 8.3: Pregnancies:

- Re-insertion of the pregnancy outcome collection for the female partners of any males which remains valid for Korea only.

IRBs/IECs

- 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 04 (20-July-2018)

Amendment Rationale

The main purpose for this amendment is to:

- Allow exploration of an additional, lower dose of MCS110 in patients with pancreatic cancer. Data generated in the dose escalation part of the study show preliminary signals of efficacy (1 PR, 2 SD >1 year) at the lowest dose level of MCS110 (1 mg/kg, Q3W) in combination with PDR001 in pancreatic cancer patients. In order to further explore this, two additional groups, each consisting of up to 20 patients with pancreatic ductal adenocarcinoma (PDAC) may be enrolled at either 1 mg/kg Q3W or the RP2D (7.5mg/kg, Q3W) of MCS110 in combination with PDR001 (300 mg, Q3W) respectively. Recruitment into these two groups will be contingent upon evidence of clinical benefit in the first 20 PDAC patients treated at the RP2D.

Additional changes to the protocol:

- [redacted]
- Add laboratory measurements during study visits. Asymptomatic CK elevations were noted in healthy volunteers and in pigmented villonodular synovitis (PVNS) patients treated with MCS110. Maximal CK elevations in PVNS patients were observed 28-43 days after a single dose of MCS100. In order to assess the dynamics of CK elevations later during the course of treatment with MCS110, additional blood chemistry samples have been added on Cycle 4 Day 8.
- Remove the requirement for use of condom for male study participants. Monoclonal antibodies are not genotoxic due to their high molecular weight, and are not expected to interact with DNA. In addition, they have a low distribution to the semen, a relatively small volume of semen delivered to the partner, and very low absorption. Fetal harm from semen delivery is therefore biologically implausible and the amount of monoclonal antibodies able to gain access to the partner's systemic circulation via trans-epidermal transfer would be expected to be extremely low. Therefore, the use of condom for male study participants is no longer required.
- Include new guidance on dose modifications for suspected immune-related adverse events. To align with recently published guidelines on the clinical management of suspected immune-related toxicities, and to provide guidance for the management of immune related acute dermatologic adverse events seen in study with PDR001, the dose modification section of the protocol and corresponding table were updated. After the recent occurrence of a case of Stevens Johnson Syndrome in a study with PDR001, the dose modification guidelines for protocols using PDR001 were updated to mandate permanent discontinuation of study treatment for patients who experience SJS or Lyell syndrome/toxic epidermal necrolysis (TEN). This change has already been implemented

as part of an urgent safety measure released on 15 June 2018. This protocol amendment is now formalizing these changes in the table describing the criteria for dose reduction/interruption and re-initiation of treatment for adverse drug reactions.

- The withdrawal of consent language was revised to differentiate sample use after a patient withdraws consent based on the different regulations/laws around the world.

Study status

The CMCS110Z2102 study is ongoing in the phase 2 part with MCS110 at 7.5 mg/kg in combination with PDR001. As of 10 April 2018, 60 patients have received the combination of MCS110 and PDR001 at doses of 1 mg/kg and 100 mg (6 patients), 3 mg/kg and 100 mg (12 patients), 3 mg/kg and 300 mg (12 patients), 5 mg/kg and 300 mg (13 patients), 7.5 mg/kg and 300 mg (6 patients), and 10 mg/kg and 300 mg (11 patients), respectively.

Changes to the protocol

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

Section 2.2: Rationale for study design

- The text was updated to reflect the change of design for PDAC patients participating Phase II.

Section 3: Objectives and endpoints

- Table 3-1 Clinical benefit rate in the pancreatic cancer disease group, added as per Amendment 3 is now clearly indicated in the table. [redacted]

Section 4.1: Description of study design

- The description of the design of Phase II was updated.
- Figure 4-1 was updated to reflect the change in study design.

Section 4.2: Timing of interim analysis and design adaptations

- The text was updated to reflect the change in the design of Phase II

Section 5.3: Exclusion criteria

- Exclusion criteria #21 was deleted as use of condom for male participants is no more required.

Section 6.3.1: Dose modification and dose delay

- The section was updated with new recommendations for the management of suspected immune-related adverse events.

Table 6-4 Dose modification for drug related toxicities

- The table was updated with new recommendations for the management of immune-related adverse events.

Table 7-1: Visit evaluation schedule

- Blood chemistry and hematology added at Cycle 4 Day 8.
- [redacted]
- [redacted]

Section 7.1.4 Withdrawal of consent

- The withdrawal of consent language was revised.

[redacted]

- [redacted]
- [redacted]
- [redacted]

Section 8.1: Adverse events

- Reference to the dose modification recommendations provided in Section 6.3.1 was added.

Section 8.3: Pregnancies

- Collection of pregnancy outcome for female partners of male participants was removed.

Section 8.5: Data Monitoring Committee

- The text was updated to reflect the change in the design of Phase II

Section 10: Statistical methods and data analysis

- It was clarified that the outputs for Group 2 in expansion will be reported by dose level, when applicable.

Section 10.4.2.2: Statistical methods and data analysis for Phase II

- Language about the Bayesian model for a lower dose group for Phase II Group 2 was added.

[redacted]

- [redacted]

Section 10.7: Interim analysis

- The text was updated to reflect the change in the design of Phase II

Section 10.8: Sample size calculation

- The sample size justification section was updated to reflect the changes in Phase II Group 2 design.

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 in this amendment identified above as being related to the USM have already been implemented by a USM letter issued on 15 June 2018. These changes are required for patient safety (i.e. necessary to eliminate immediate hazards to the trial subjects ICH GCP 3.3.8). Therefore they were required to have been implemented prior to IRB/IEC approval of this amendment.

All other 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 03 (14-Feb-2018)

The main purpose for this amendment is to:

1. Increase the number of pancreatic cancer patients to be enrolled in the Phase II part of the study from 20 to 40
2. Change the primary endpoint for antitumor activity in pancreatic cancer from overall response rate (ORR) to clinical benefit rate (CBR)

[redacted]

4. Mention that statins should be used with caution.

These changes are proposed for the following reasons:

- Preliminary data (data cut-off 24-Nov-2017) from this study show encouraging clinical activity in advanced pancreatic patients treated at a range of doses in dose escalation, with long-lasting clinical benefit (confirmed objective response or SD>4 months) in 2 of 30 evaluable patients per RECIST v1.1. Evaluable patients are defined as patients with at least 1 post-baseline efficacy assessment or has discontinued study treatment. Per irRC, there is one patient who showed pseudo-progression per RECIST, but achieved SD > 4 months. Therefore, under irRC, there is a 10% long-lasting clinical benefit in 3 out of 30 advanced pancreatic patients. To allow further exploration of anti-tumor activity of the combination in this patient population, approximately 40 patients will be enrolled in the Phase II pancreatic cancer group. [redacted]
- Recent clinical data demonstrate that combined blockade of CSF-1R and PD-1 results in a long lasting (6 to 9 + months) objective response rate and clinical benefit rate (CBR) of 13% and 16%, respectively, in patients with advanced pancreatic cancer (Wainberg *et al.,* 2017). Given that objective responses are rare in advanced pancreatic cancer and that long lasting stable disease is considered beneficial to patients, the primary endpoint for antitumor activity in this study will be changed from objective response to clinical benefit rate (confirmed objective response or SD>4 months).
- [redacted]
- Statins are known to be frequently associated with CK elevations and transient CK elevations were noted in healthy volunteers and patients studies with MCS110.

Study status

The CMCS110Z2102 study is ongoing in the dose escalation part of the study. As of 29 January 2018, 56 patients have received the combination of MCS110 and PDR001 at doses of 1 mg/kg and 100 mg (6 patients), 3 mg/kg and 100 mg (12 patients), 3 mg/kg and 300 mg (12 patients), 5 mg/kg and 300 mg (13 patients), 7.5 mg/kg and 300 mg (6 patients), and 10 mg/kg and 300 mg (7 patients), respectively.

Changes to the protocol

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

Section 2.2: Rationale for study design

- The text was updated to specify that clinical benefit rate will be evaluated in approximately 40 patients in the pancreatic cancer group

Section 3: Objectives and endpoints

- Table 3.1 was updated to mention clinical benefit rate in the pancreatic cancer disease group, [redacted]

Section 4.1: Description of study design

- The text is updated to mention that 40 pancreatic cancer patients will be enrolled
- Figure 4.1 is updated to reflect the change in study design.

Section 4.2: Timing of interim analysis and design adaptations

- The text is updated to reflect the change introduced between pancreatic cancer and other disease group.

Section 6.4.1: Permitted concomitant therapy requiring caution and/or action

- Statins are mentioned as to be used with caution

Table 7.1: Visit evaluation schedule

- [redacted]
- [redacted]

Section 10.4.1: Variables

- Clinical benefit rate is defined as the primary efficacy variable for the pancreatic cancer group, while overall response rate remains the primary efficacy variable for the other cancer groups.

Section 10.4.2.2: Phase II

- The text has been updated to differentiate between pancreatic cancer group (Group 2) and other groups (groups 1, 3 and 4).
- Parameters of priors of BLRM are defined for clinical benefit rate in pancreatic cancer patients.

Section 10.5.2: Other secondary efficacy objectives

- Duration of stable disease of 4 months is defined for clinical benefit

10.8: Sample size calculation

- Pancreatic cancer is deleted from table 10-2 and a new table 10-4 is introduced for pancreatic cancer

13: References

- The list of references was updated

14.3: recommended management algorithms for suspected toxicities

- Management of neurological adverse events is now mentioned

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 02 (07-Feb-2017)

The main reasons for this amendment are to make changes requested by the Health Authorities (HA), to prepare the protocol for inclusion of Japanese patients and to update safety monitoring. Furthermore, clarifications and correction of typos have been made to the protocol.

As requested by HA, patients with active tuberculosis, interstitial lung disease or non-infectious pneumonitis or history of drug induced interstitial lung disease will be excluded from enrolment in the study. Additionally, a washout period of 7 days for immunosuppressive therapy and corticosteroids will be required before starting study treatment. Furthermore, country-specific wordings have been added to the protocol to allow Japanese patients to participate in the phase II part of the study. In accordance with HA requirements, Japanese patients will remain inpatients during the first treatment cycle and will have repeat chest X -rays performed at baseline and after one week of treatment.

Given that Grade 1-2 adverse events, possibly related to cytokine release (fever, weight gain and pleural effusion) have been observed during study treatment, an extended immune modulation marker panel will be assessed at any safety events suspected to be related to cytokine release to further characterize these events. In addition, urinalysis to evaluate possible protein leakage will be performed for all patients at the beginning of each treatment cycle. Furthermore, since the safety follow-up period after PDR001 treatment was extended from 90 to 150 days in the last amendment, additional safety follow-ups will be performed at 30 and 90 days. To add flexibility all safety follow-ups may be performed by phone. Consequently, the protocol-specified lab tests or visits will not be requested during the safety follow-up period.

This protocol amendment clarifies [redacted] the definition of post-menopausal status, corrects the imaging assessment schedule [redacted] Lastly, the criteria for Hy's law has been corrected in Table 6-3 Criteria for defining dose-limiting toxicities.

Study status

The CMCS110Z2102 study is currently enrolling. As of 12th January 2017, seventeen patients have received the combination of MCS110 and PDR001 at doses of 1 mg/kg and 100 mg (6 patients) and 3 mg/kg and 100 mg (11 patients), respectively. No drug limiting toxicities were observed at this date.

Changes to the protocol

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

- Table 1-1 was updated with information of the ongoing phase 1 study in Japan.
- [redacted]
- Section 5.2: Inclusion criteria 2 was updated with text specific for Japan.

- Section 5.3: Exclusion criteria 6 was updated to specify that patients with active tuberculosis are excluded from the study. Exclusion criteria 10 was updated to specify that patients with interstitial lung disease, non-infectious pneumonitis, history of drug induced interstitial lung disease or history of immune related adverse events are excluded from the study. The requirement of a washout period of 7 days for immunosuppressive treatment and corticosteroids was added to exclusion criteria 12. Repeat text was deleted from exclusion criteria 18. Definition of post-menopausal status was updated in exclusion criteria 20.
- Table 6-3: The typo in the definition dose limiting toxicity linked with bilirubin increase was corrected.
- Section 6.3.3 : Management of anticipated risks were further clarified
- Section 7.1 : Japanese patients will need to stay hospitalized during the first cycle of treatment
- Table 7-1 was updated to delete the optional tests planned during the safety follow up visits.
- Table 7-1 and section 7.2.2.5.3 were updated to include regular urinalysis testing.
- Section 7.2.1: The imaging assessment schedule was corrected to be performed until week 51 after start of treatment to align with the assessment schedule in patients still on treatment.
- [redacted]
- [redacted]
- Section 7.1.5, the definition of safety follow-up, disease progression follow-up, and survival follow-up periods were clarified. Phone contacts with the patients are now requested also on day 30 and 90 after treatment discontinuation.
- Section 7.2.2.1 : oxygen saturation will be measured with vital signs in Japanese patients
- Table 7-4 was updated to reflect that an extended cytokine panel will be tested in case of adverse event suspected to be related to cytokine release. [redacted]
- Section 7.2.2.7 : chest x-ray will be performed in Japanese patients at screening and Day 8 of Cycle 1
- Section 8.2.2 was updated with language specific for Japan.
- Groupings for safety analysis was updated under Section 10.4.2.1.2.
- Section 11.5 was updated to better describe Novartis publication policy

IRB/IEC/HA Approval

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 01 (11-Jul-2016)

Amendment rationale

The main reason for this amendment is to add more specific guidance for dose modifications and to revise definitions for dose limiting toxicities (DLTs), following Health Authority (HA) feed-back. In addition the routine chemistry lab test Lactate dehydrogenase (LDH) has been added since a recent publication suggest that TNBC and metastatic melanoma patients with aggressive tumor growth, with elevated LDH, may have less benefit of PD-1 inhibition compared to those with more slowly growing tumors (Diem et al., 2016, Nanda et al., 2016).

[redacted]

With the available PK data obtained from the single agent first-in-human study CPDR001X2101, an exploratory population PK (PopPK) analysis showed that the T1/2 of PDR001 in man is 20 [17, 23] days (mean [90% CI]). Using five times the upper limit of the half-life of 23 days and an added safety margin, the protocol is amended to increase the duration of contraception and safety follow-up periods post PDR001 treatment from 90 days to 150 days. These changes are related to an Urgent Safety Measure communicated on 08-June-2016 to all investigators.

Minor corrections of typos/clarifications of text were also made. The details are provided in the below section “Changes to the protocol”.

Study status

The CMCS110Z2102 study is currently under review by Health authorities .

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 6.1.1 Dosing regimen. Adding instructions to resume treatment at a lower level after skipping an administration (if meeting criteria for DLT)
- Section 6.2.4 Definitions of dose limiting toxicities. The following Grade 4 AEs should be defined as DLTs: Electrolyte abnormalities and CK elevation
- Section 6.3.1 Dose modification and dose delay. Update of dose modification recommendations for drug related toxicities and instructions to reduce dose after DLT.
- Section 4 Study design, and Section 7.1.5 Follow-up period. Update of the safety period duration
- Section 7.2.2.5 Laboratory evaluation: LDH was added in the list of clinical laboratory parameters to be analyzed.
- Information about update of the follow-period duration were inserted in Section 5.3, Section 6.3.2., Section 7.2.2.5.8, Section 8.1.1, Section 8.2.2, Section 10.4.2 and Table 7-1.

1 Background

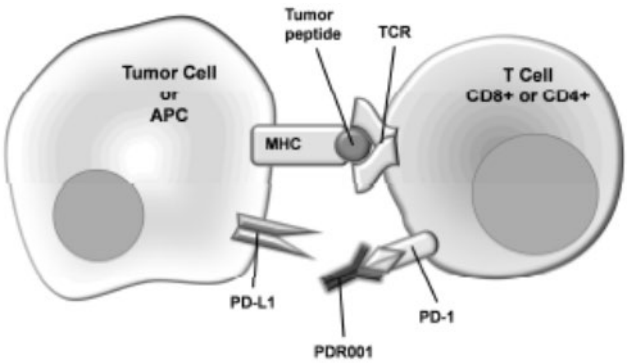
1.1 Overview of disease pathogenesis, epidemiology and current treatment

Immunotherapies that target immune checkpoints are currently emerging as key agents in cancer therapy. Antibodies inhibiting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-1 (PD-1) demonstrate strong efficacy, durable antitumor effects and an acceptable safety profile. Response to checkpoint inhibition differs strongly across tumor types, with highest rates of response observed in advanced melanoma. Both non-responsiveness to checkpoint inhibition as well as initial response followed by progression have been observed, indicating the presence of *intrinsic resistance* and therapy-induced *acquired resistance* (Kelderman 2014). Tumor associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) are among the most abundant immune cells in the tumor microenvironment and are known to mediate therapeutic resistance in cancer (Jiang 2015, Ruffell 2015). Thus, immune escape mediated by TAMs and MDSCs is a potential cause of limited clinical benefit of immune check-point blockade (Zhou 2014). Recently, a clinical study showed an association between circulating MDSCs and intrinsic resistance to PD-1 inhibition in melanoma patients (Zhou 2014, Weber 2015). Additionally, preclinical studies show that single agent blockade of CSF-1/CSF-1R or PD-1 results in limited efficacy by restraining tumor growth, but combined blockade of CSF-1R and PD-1 potently elicits tumor regressions (Zhu 2014). Currently, several clinical studies are ongoing evaluating the efficacy of dual targeting of PD-1 and TAMs, supported by synergistic antitumor activity demonstrated in a preclinical pancreatic cancer model (Zhou 2014).

1.1.1 Overview of PD-1

PD-1 is a critical co-inhibitory receptor that is upregulated on T cells upon activation (Freeman 2008). It is also expressed by B cells, NK cells, dendritic cells, and activated monocytes. The ligands for PD-1, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), are expressed by macrophages and monocytes, and can be induced on numerous cell types (T cells, endothelial cells, and tumor cells) during inflammation (Keir 2008). Engagement of PD-1 by its ligands transduces a signal that inhibits T-cell proliferation, cytokine production, and cytolytic function (Riley 2009). During tumorigenesis, cancer cells from a wide range of tumor types exploit immune checkpoint pathways, such as PD-1, to avoid detection by the adaptive immune system (Murphy 2011). Blockade of the PD-1 pathway has been shown to lead to both accumulation and increased activity of antitumor effector T cells and reduced numbers of regulatory T cells (Tregs) at the tumor site (Wang 2009, Mangsbo 2010, Mkrtichyan 2011, Rosenblatt 2011).

Figure 1-1 Blockade of PD-1/PD-1 interaction by PDR001

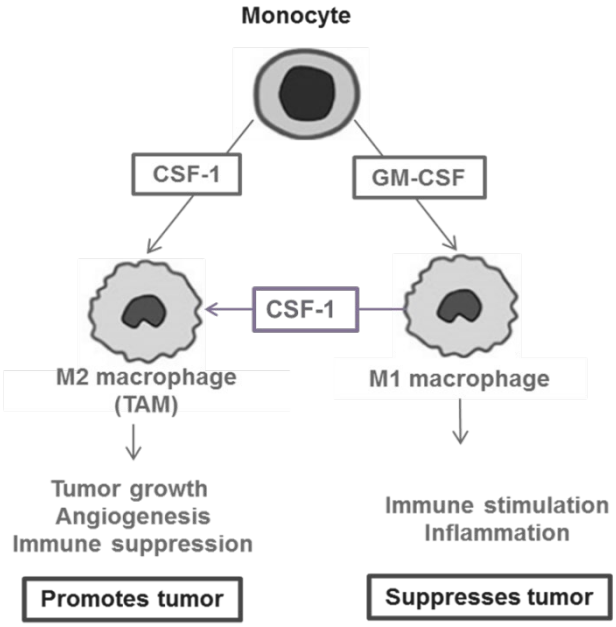


APC: antigen presenting cell; MHC: major histocompatibility; TCR: T cell receptor

1.1.2 Overview of CSF-1

CSF-1, also known as macrophage colony-stimulating factor (M-CSF) is a protein that is produced by several cell types and tissues, including various cancer cell types (Aharinejad 2007, Priceman 2010, Tarhini 2012). CSF-1 binds to the tyrosine kinase receptor, CSF-1 receptor (CSF-1R), on myeloid cells, which results in increased proliferation and differentiation of myeloid cells into type M2 macrophages (TAMs) and MDSCs, and recruitment into tumors (Dai 2001, Li 2006). TAMs and MDSCs use several mechanisms to induce T-cell inhibition; directly through PD-L1 and indirectly through secretion of IL-10, leading to an immunosuppressive tumor environment (Gabrilovich 2009, Kuang 2009, Ruffell 2015).

Figure 1-2 Macrophage polarization and function



Modified figure from Sica 2006. TAMs induce T-cell inhibition resulting in immune suppression.

Preclinical and clinical studies demonstrate that blockade of CSF-1 or CSF-1R activates the immune system by limiting tumor infiltration by TAMs and MDSCs, or altering macrophage polarization, resulting in significantly enhanced antigen presentation and an increase in CD8+ T-cells (DeNardo 2011, Pyonteck 2013, Ruffel 2014, Ries 2014, Zhou 2014). However, inhibition of CSF-1 signaling upregulates checkpoint molecules, including PDL1 and CTLA4, thereby limiting the potential beneficial therapeutic effects (Zhu 2014).

1.2 Introduction to study treatment

1.2.1 Overview of PDR001

PDR001 is a high-affinity, ligand-blocking, humanized anti-PD-1 IgG4 antibody that blocks the binding of PD-L1 and PD-L2 to PD-1. PDR001 recognizes PD-1 in cynomolgus monkeys and shows functional activity *in vitro* and *ex vivo*. For further details, please refer to the [PDR001 Investigator's Brochure].

1.2.1.1 Non-clinical experience of PDR001

PDR001 binds specifically and with high affinity to human PD-1. In Biacore assays, the constant of dissociation (K_D) of PDR001 on human PD-1 is 0.827 nM. In *ex vivo* lymphocyte stimulation assays using human blood, PDR001 enhances interleukin-2 (IL-2) production by approximately 2 fold in response to super antigen stimulation with Staphylococcal enterotoxin B (SEB). PDR001 does not cross-react with rodent PD-1, and thus, cannot be evaluated in murine tumor models. It does cross-react with cynomolgus monkey PD-1, and is functionally active, making cynomolgus monkey a relevant species for toxicology studies. The affinity of PDR001 for cynomolgus PD-1 is 0.929 nM, nearly the same for human PD-1, as noted above.

A GLP tissue cross reactivity study using frozen human and cynomolgus monkey tissues was also done in support of the safety of PDR001. There was no unexpected binding observed. The non-clinical toxicology of PDR001 was evaluated in a five week GLP toxicology study in cynomolgus monkeys with safety pharmacology endpoints and an eight week recovery. All main phase data as well as recovery pathology data are reported here. All other recovery phase data are pending. Repeat administration of PDR001 to monkeys was well tolerated at all doses tested in the GLP toxicology study. No test article-related in-life, mortality, organ weight changes, or macroscopic findings were noted. There were no PDR001-related effects seen in any of the safety pharmacology endpoints assessed (cardiovascular, neurobehavioral, and respiratory). Macrophage infiltrates into the splenic white pulp were observed in animals given 100 mg/kg/week and mononuclear cell infiltrates, often associated with fibrosis, were also observed around the injection site blood vessel (saphenous vein) in a few animals given ≥25 mg/kg/week. These PDR001-related microscopic changes were fully reversible after an eight week recovery period.

The following changes were noted in main phase and recovery treated animals as well as control recovery animals. Mostly low grade changes were noted in several tissues in the form of mononuclear infiltrates in the vascular and perivascular space. In general, in most organs, vascular/perivascular changes were limited to one or a few blood vessels in each organ and sometimes involved a segment of a blood vessel with occasional vessel wall degeneration. No evidence of parenchymal damage was associated with the vascular/perivascular changes in any

of the organs examined and the changes were not associated with any frank tissue injury. While these effects were not exclusive to treated animals, because of their nature and close association with the expected pharmacology of PD-1 blockade, a potential PDR001 related effect cannot be excluded. There were no test article related effects seen in the cardiovascular assessments. All other microscopic findings were considered spontaneous or otherwise unrelated to PDR001 administration.

Dose-dependent exposure to PDR001 in each dose group was confirmed. A pharmacodynamic *ex vivo* superantigen stimulated whole blood assay measuring IL-2 release was performed. Blood from untreated control animals showed augmentation of IL-2 release when PDR001 was added *ex vivo*, whereas blood from treated animals at all doses did not show augmented IL-2 release, indicating target engagement and inability to further dis-inhibit the SEB induced response with the further addition of PDR001. The Highest Non-Severely Toxic Dose (HNSTD) in this study was 100 mg/kg. PDR001 has a favorable safety profile in monkeys that supports a projected human starting dose of 1 mg/kg in the first in human study [CPDR001X2101]. For further details, please refer to the [PDR001 Investigator's Brochure].

1.2.1.2 Clinical experience of PDR001

PDR001 is being tested in a FIH, multi-center, open-label study [CPDR001X2101] starting with a Phase I dose escalation part, followed by a Phase II part.

The [CPDR001X2101] study started enrollment on 27 April 2015 and is ongoing. As of 17 December 2015, a total of 58 patients had been treated in the study at the dose levels of 1, 3 and 10 mg/kg Q2W and 3 and 5 mg/kg Q4W. No patient experienced a dose limiting toxicity (DLT) and the toxicity profile appears to be similar to that of marketed inhibitors of PD-1. The PK data obtained from the dose escalation, and modeling of the exposure data, support the use of flat dosing for PDR001 of 400 mg given every 4 weeks. The expected PDR001 C_{trough} concentrations are in line with observed steady state mean C_{trough} concentrations for pembrolizumab, which is approved with substantial efficacy in several cancer types. The data also support the use of 300 mg Q3W as an alternative dose regimen if it is more convenient for scheduling purposes, for example in combination treatment regimens.

1.2.2 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 inhibiting its effect on monocytes and macrophages. See [MCS110 Investigator's Brochure] for further information.

1.2.2.1 Non-clinical experience of MCS110

The ability of MCS110 to neutralize the activity of CSF-1 was established in several *in vitro* and *in vivo* studies.

The preclinical pharmacokinetics (PK) and pharmacodynamics (PD) of MCS110 were evaluated in cynomolgus monkeys following a 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.

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 with systemic administration. 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 (LDH), 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 with 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).

Please refer to the most recent edition of the [MCS110 Investigator's Brochure] for further information.

1.2.2.2 Clinical experience

Four clinical trials with MCS110 have been initiated. Brief information on clinical experience of relevant MCS110 studies is provided below. For additional information, please refer to [MCS110 Investigator Brochure].

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
[MCS110Z2201] Ongoing	Efficacy study	Safety, tolerability, PK/PD, efficacy	Triple Negative Breast Cancer (TNBC), n=24	10 mg/kg iv infusions every 21 days (additional dose C1D8)
[MCS110Z1101] (ongoing)	Healthy volunteers, dose escalation in Japanese population	Safety, tolerability, PK/PD	Japanese healthy male, n= 21	1,3,5,10mg/kg iv infusion single dose.

1.2.2.2.1 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 (Grade 1 to Grade 4) 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 (Grade 1), 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 pharmacokinetics (PK), with decreasing clearance (CL) and increasing mean residence time (MRT) or effective $t_{1/2}$ 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 are 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 a 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 a plateau at the single-dose level at or above 10 mg/kg, and it was 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 doses at or above 5 mg/kg and minimal at doses at or below 1 mg/kg.

1.2.2.2.2 CMCS110X2201, a Phase II study in pigmented villonodular synovitis

[CMCS110X2201] is an ongoing Phase II study designed to evaluate safety, tolerability and efficacy of MCS110 in pigmented villonodular synovitis (PVNS). PVNS is a benign tumor consisting of macrophages and multinucleated giant cells, most commonly located to joints. As of 19-Feb-2015, 16 patients with PVNS have been treated with MCS110. In Part A of the study, 7 patients received a single dose of 10 mg/kg MCS110. In the multiple dose part B of the study, at the cut-off date of 19-Feb-2015, 9 patients were randomized and had received at least one infusion.

Clinical safety and tolerability

As of February 19 2015, the most common adverse events reported include elevated CK (Grade 2-4), periorbital edema (Grade 1) and AST elevations (Grade 1).

Clinical pharmacokinetics

PK analysis is ongoing. Preliminary data of the first 3 patients with single i.v. infusion of 10 mg/kg in the ongoing study suggested a similar PK profile as that observed 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 return to baseline.

Clinical efficacy

Efficacy data from four PVNS patients receiving a single dose of 10 mg/kg MCS110 demonstrated a clear efficacious effect with a mean reduction in tumor volume of 40%.

1.3 Overview of combination treatment

1.3.1 Non-clinical

No preclinical data exist for the combination of MCS110 and PDR001.

1.3.2 Clinical

No clinical data exist for the combination of MCS110 and PDR001. However, several clinical studies are ongoing evaluating the efficacy of dual targeting of PD-1/PD-L1 and TAMs in advanced malignancies (ClinicalTrials.gov: [NCT02452424], [NCT02526017], [NCT02323191]).

1.3.3 Potential for drug-drug interactions

Specific studies to investigate drug-drug interactions (DDI) have not been conducted. MCS110 and PDR001 are monoclonal antibodies, not metabolized by Cytochrome P450 (CYP450) enzymes or transported by P-glycoprotein (PgP) or related ABC membrane transporters. Therefore DDIs at the level of these enzymes and transporters are not expected. MCS110 specifically neutralizes CSF-1 and is not expected to modulate cytokines. Cytokines produced by PDR001-activated lymphocytes may impact levels of PgP or CYP450 enzyme activity. The clinical relevance of this is unknown but considered unlikely.

1.3.4 Expected overlapping toxicities

PD-1 inhibitors are known to cause immune mediated adverse events e.g. pneumonitis, colitis etc, whereas no apparent immune related adverse events have been reported with MCS110 and other CSF-1/R targeting drugs (USPI/SPC nivolumab/pembrolizumab; Cassier ASCO 2014, Rugo ESMO 2014). However, since both MCS110 and PDR001 are immune activating drugs there is a potential risk for higher frequency or aggravation of immune mediated adverse events.

As of 03-Sep-2015, no liver enzyme elevations have been reported from treatment with PDR001 [CPDR001X2101], nonetheless, liver enzyme elevations and immune related hepatitis have been reported with other PD-1-inhibitors and a class effect should be suspected, (USPI/SPC nivolumab/pembrolizumab). Clinical studies with MCS110 report frequent asymptomatic and transient CK (Grade 3) and AST elevations (Grade 1-2), whereas ALT elevations (< Grade 1) were only seen in occasional patients. The increase of enzymes did not reflect muscle damage since markers for cardiac or skeletal muscle damage were evaluated and found to be normal. Isolated CK/AST elevation (without ALT elevation) is not considered to be consistent with liver damage (Krishnamurthy 2009). The elevation of CK and liver transaminases is considered a pharmacological effect of MCS110 due to reduction in the number of liver macrophages (Kupffer cells) responsible for elimination of these enzymes from circulation. Nonetheless, overlapping liver enzyme elevations may be expected with the combination treatment of MCS110 and PDR001, therefore liver enzymes will be carefully monitored in this study.

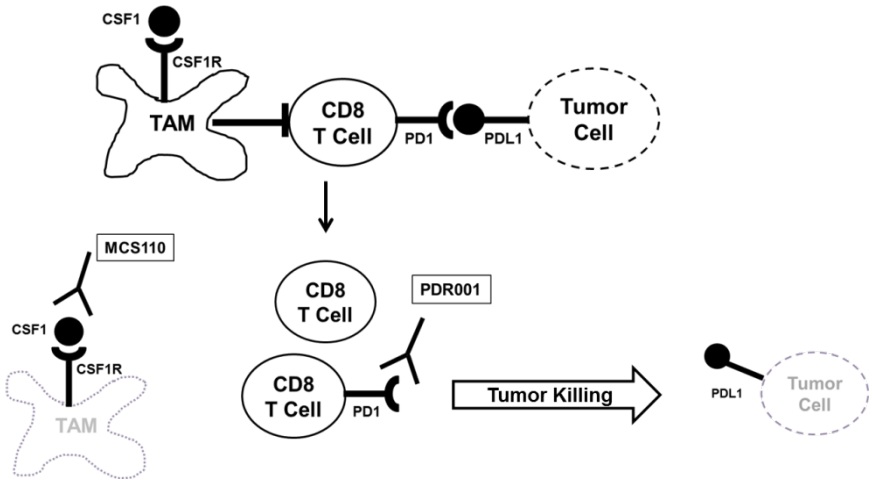
Skin toxicity have been reported from studies with CSF-1/R inhibitors as well as PD-1 inhibitors; thus, skin toxicity may be an overlapping toxicity with the study drug combination (USPI/SPC nivolumab/pembrolizumab; Cassier ASCO 2014, Rugo ESMO 2014).

2 Rationale

2.1 Study rationale and purpose

Treatment with PD-1 checkpoint inhibitors results in clinically important anti-tumor activity in several tumor types (Topalian 2014, Gettinger 2015, Rizvi 2015). However, intrinsic as well as acquired resistance to PD-1 inhibition has been observed (Section 1.1). Therapeutic resistance to various cancer treatments, including PD-1 inhibition, is mediated through immunosuppressive cells (TAMs and MDSCs) in the tumor microenvironment (Ruffell 2015, Weber 2015). Preclinical and clinical studies have demonstrated that tumor infiltrating M2 macrophages (TAMs) can be depleted or polarized into M1 macrophages by CSF-1 signaling blockade (Figure 1-1, DeNardo 2011, Pyonteck 2013, Ruffel 2014, Ries 2014). Furthermore,combined targeting of PD-1 and CSF-1 signaling resulted in synergistic antitumor activity in a preclinical pancreatic cancer model (Zhou 2014).

Figure 2-1 Rationale for combined treatment with PDR001 and MCS110



TAMs induce T-cell inhibition leading to an immunosuppressive tumor environment (Gabrilovich 2009, Kuang 2009, Ruffell 2015). Tumor cells exploit immune checkpoint pathways to inhibit T-cell proliferation and avoid detection by the immune system (Murphy 2011). Combined treatment with MCS110 and PDR001 is expected to result in TAM depletion, enhanced T-cell activation and synergistic antitumor activity in the clinical setting.

Combined treatment with MCS110 and PDR001 will be evaluated in disease indications where single agent PD-1/PD-L1 inhibition did not result in clinically meaningful responses and therapeutic resistance may be mediated by TAMs:

1. Anti-PD-1/PD-L1 treatment **naïve** TNBC, pancreatic and endometrial cancer

Clinical studies show modest, but limited response to PD-1/PD-L1 inhibition in TNBC and pancreatic cancer indicating *intrinsic resistance* (Nanda 2014, Emens 2015, Segal 2014). Additionally, TNBC, pancreatic and endometrial cancers are characterized by an immune suppressive tumor microenvironment consisting of a high content of TAMs, known mediators of intrinsic drug resistance (Yuan 2014, Mielgo 2013, Kübler 2014).

2. Anti-PD-1/PD-L1 treatment **resistant** melanoma

Clinical studies show high response rates to PD-1/PD-L1 inhibition in melanoma; however, non-responsiveness (*intrinsic resistance*) as well as initial response followed by progression (*acquired resistance)* have been observed (Topalian 2014). Clinical data demonstrate that MDSCs mediate intrinsic resistance to PD-1 inhibition in melanoma (Weber 2015).

The purpose of this study is to evaluate the safety, tolerability and efficacy of combined treatment with MCS110 and PDR001. In addition, the mechanisms of intrinsic and acquired resistance to PD-1/PD-L1 inhibition as well as the ability of MCS110 to overcome resistance will be explored.

2.2 Rationale for the study design

This is an open-label, Phase Ib/II study of the combination of MCS110 and PDR001. The study consists of two parts: a dose escalation in the Phase Ib part and a Phase II part where four groups will be treated at the recommended Phase II dose (RP2D).

Phase Ib

In the Phase Ib part, cohorts of patients will receive escalating doses of MCS110 and PDR001 until a MTD/RP2D is identified. The dose escalation decision will be guided by a Bayesian logistic regression model (BLRM) with overdose control (EWOC) principle based on DLT data in the context of available safety, PK and PD information. For details of the dose escalation, please refer to Section 6.2.

This open-label dose escalation study design using a BLRM is a well-established method to estimate the MTD, or identify a lower RP2D in cancer patients. The adaptive BLRM with EWOC principle controls the risk of DLT in future patients on study. The decisions on the dose of MCS110 in combination with PDR001 are made by the Investigators and Novartis study personnel and will be based upon the dose identified to satisfy the EWOC criterion under the appropriate BLRM, patient tolerability and safety, PK and PD data available at the time of the decision Section 6.2.3.

Phase II

The Phase II part of the study will begin after the RP2D is determined for the combination of MCS110 and PDR001. The primary objective of the Phase II part is to estimate the preliminary anti-tumor activity of MCS110 in combination with PDR001 in diseases known to respond to PD-1/PD-L1 inhibition or where limited response may be attributed to immune escape mediated by the tumor microenvironment (TAMs, MDSC). These disease indications include melanoma, TNBC, endometrial and pancreatic cancer.

The efficacy of the combination will be explored both in patients that are naïve to anti-PD-1/PD-L1 treatment (TNBC, pancreatic, endometrial cancer) and patients that have progressed on previous anti-PD-1/PD-L1 treatment (melanoma). Twenty patients are expected to be enrolled in each of the TNBC, endometrial and melanoma groups, but enrollment will be expanded up to approximately 40 patients in those groups in which objective responses (CR or PR) are observed (≥ 3 of 20 patients in the anti-PD-1/PD-L1 naïve groups or ≥ 2 of 20 patients in the anti-PD-1/PD-L1 resistant groups). In addition, 20 patients will be enrolled in the pancreatic group at RP2D. Enrollment may be expanded up to approximately a total of 40 patients at RP2D in this group if at least 3 pts with CR, PR or SD > 4 months are observed (addition of Group 2a, see Figure 4-1). Further, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criteria are met (Group 2b, see Figure 4-1).

A Bayesian design will be used to estimate the overall response rate (ORR) in each of the TNBC, endometrial and melanoma groups and the clinical benefit rate (CBR) in the pancreatic group. For Group 2 (pancreatic cancer), a separate model with same prior assumptions will be used to estimate CBR for the different dose levels. The Phase II groups are designed to detect efficacy signals indicating a patient population where further studies of the combination of MCS110 with PDR001 are warranted.

2.3 Rationale for dose and regimen selection

PD-1 inhibition has demonstrated objective responses in several different malignancies, whereas blockade of CSF1/R signaling has led to TAM depletion and immune activation, but no objective responses have been reported so far (Ries 2014, Gomez-Roca 2015). The PDR001 dose will start at 100 mg, a dose expected to demonstrate antitumor activity, and MCS110 will start at 3 mg/kg. These doses were selected based on preclinical and clinical studies as described in Section 6.2.1. Both antibodies will be administered via i.v. infusion every 3 weeks in accordance with ongoing studies of MCS110 combined with chemotherapy [CMCS110Z2201] and single agent PDR001 [CPDR001X2101].

2.4 Rationale for choice of combination drugs

Currently, nivolumab and pembrolizumab are the only PD-1 inhibitors approved by FDA and EMA for the treatment of advanced melanoma and non-small cell lung cancer; however, none are approved for the treatment of TNBC, pancreatic cancer or endometrial cancer. PDR001 is Novartis' PD-1 inhibitor currently being evaluated in various advanced malignancies [CPDR001X2101]. Therapeutic resistance to PD-1 inhibitors seems to be mediated through TAMs (Weber 2015). Several compounds directed towards CSF-1/CSF-1R have been reported to deplete TAMs in preclinical and clinical studies (Ries 2014, DeNardo 2011); however, none of these compounds are approved yet. MCS110 is Novartis' anti-CSF-1 antibody currently being evaluated in several studies in PVNS and TNBC. Refer to Section 1.1 and Section 2.1.

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
Phase Ib part: To characterize the safety and tolerability of MCS110 given in combination with PDR001 and to identify a recommended dose combination for Phase II.	Frequency, severity and seriousness of AEs, laboratory abnormalities and other safety parameters. Dose interruptions, reductions, and dose intensity. Incidence rate of DLTs during the first two cycles of study treatment.	
Phase II part: To estimate the anti-tumor activity of the combination of MCS110 with PDR001	-Overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (groups 1, 3 and 4). -Clinical benefit rate (CBR) per Response Evaluation Criteria in Solid Tumors (RECIST v1.1), which is defined as confirmed objective response or SD>4 months. (Group 2)	
Secondary		Refer to Section 10.5
Phase Ib part: To estimate the preliminary anti-tumor activity of the combination of MCS110 with PDR001	ORR, progression free survival (PFS), CBR,duration of response (DOR) and disease control rate (DCR) per RECIST v1.1 and per immune related Response Criteria (irRC)	
Phase II part: To further characterize the safety and tolerability of MCS110 given in combination with PDR001	Frequency, severity and seriousness of AEs, laboratory abnormalities and other safety parameters.	
Phase II part: To evaluate the preliminary anti-tumor activity of the combination of MCS110 with PDR001 by additional efficacy measures	ORR per irRC, PFS, DOR, DCR, CBR per RECIST v1.1 and per irRC (Group 1, 3 and 4) CBR per irRC, PFS, DOR, DCR, ORR per RECIST v1.1 and per irRC (Group 2)	
Phase Ib and Phase II parts: To characterize the pharmacokinetics of MCS110 and PDR001 in combination	Serum concentration of MCS110 and PDR001 and PK parameters	
To assess immunogenicity of MCS110 and PDR001	Presence and/or concentration of anti-PDR001 or anti-MCS110 antibodies	
To describe survival with MCS110 and PDR001 in combination	Overall survival (OS)	

4 Study design

4.1 Description of study design

This study is a Phase Ib/II, multi-center, open-label study starting with a Phase Ib dose escalation part followed by a Phase II part. MCS110 and PDR001 will be administered i.v. every three weeks (Q3W) until the patient experiences unacceptable toxicity, progressive disease as per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients should not discontinue treatment based on progressive disease per RECIST v1.1. The study design is summarized in Figure 4-1.

Phase Ib part

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

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

Phase II part

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

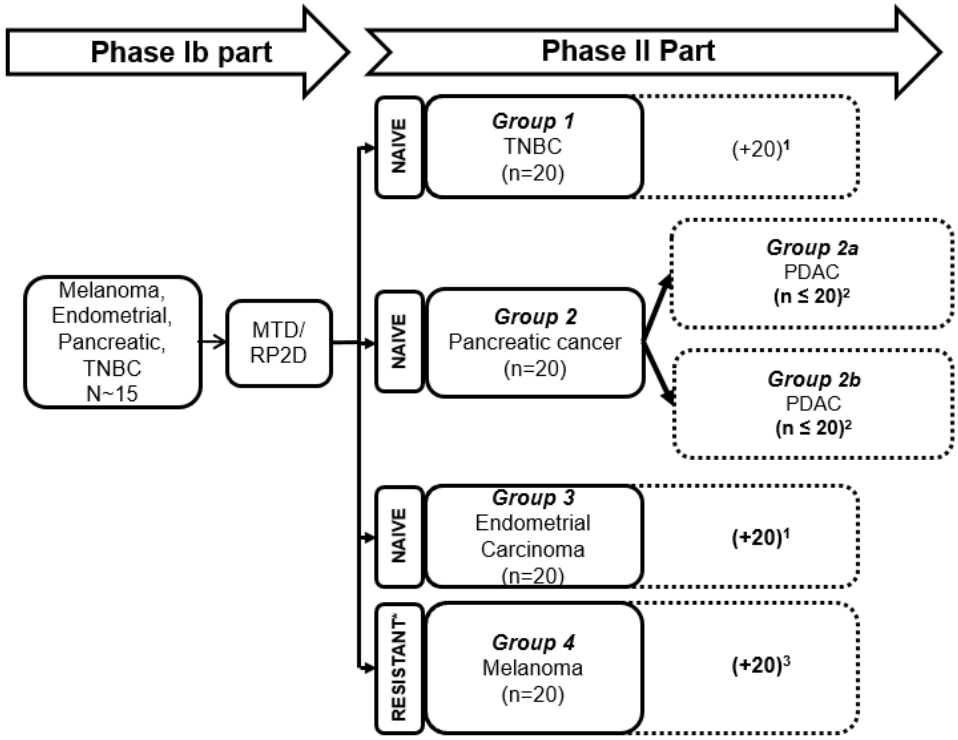
In the Phase II part, patients will be assigned to different groups depending on the tumor type as shown in Figure 4-1. Please refer to Section 5.1 for further details.

All groups will enroll approximately 20 patients each initially. Enrollment to any of these groups may be stopped at fewer patients if achieving these enrollment targets is not logistically feasible.

For Groups 1 and 3, the sample size may be extended to approximately 40 patients, if at least 3 patients out of the first 20 treated in that group have an objective response (CR or PR) per RECIST v1.1 or irRC. Twenty patients will be enrolled into Group 2 at RP2D. Enrollment may be expanded up to approximately 40 patients if clinical benefit per RECIST v1.1 or irRC (CR, PR or SD > 4 months) is observed in at least 3 pts (addition of Group 2a, see Figure 4-1). In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criteria is met (Group 2b, see Figure 4-1). Group 4 may similarly be expanded if at least 2 patients out of the first 20 treated in that group have an objective response (Figure 4-1). A Bayesian design will be used

in order to estimate ORR within each expansion group. Details of the sample size calculations leading to the patient numbers are provided in Section 10.8.

Figure 4-1 Study design



(1) In Group 1 and 3, additional 20 patients will be enrolled if ≥ 3 of 20 naive patients have an objective response.
(2) In Group 2, two parallel cohort of 20 patients will be opened if ≥ 3 of 20 naive patients have a clinical benefit. Patient in Group 2a will receive MCS110 at the dose of 1 mg/kg together with PDR001 300mg, while patients in Group 2b will receive the two drugs at the dose of 7.5 mg/kg and 300 mg respectively.
(3) In Group 4, additional 20 patients will be enrolled if ≥ 2 of 20 resistant patients have an objective response.

** Resistant= prior treatment with anti-PD1/PDL1 followed by progression. Includes patients with intrinsic (no response) and acquired (prior response) resistance.*

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

Screening period

The screening period begins once the patient has signed the study informed consent. Patients will be evaluated against study inclusion and exclusion criteria (Table 7-1 and Section 5.2, Section 5.3 and Section 7.1.1).

[redacted]

Treatment period

The treatment period will begin on Cycle 1 Day 1. For the purpose of scheduling and evaluations, a treatment cycle will consist of 21 days.

Further details are provided in Table 7-1 and Section 7.1.2.

Follow-up (FU) period

Patients will be followed up for safety evaluations 150 days after the last administration of PDR001. For patients who had to stop PDR001 treatment but continued taking MCS110 at the time of treatment stop, the follow-up evaluation will take place 90 days after the last administration of MCS110 or 150 days after the last administration of PDR001, whichever duration is longer (Table 7-1 and Section 7.1.5).

Disease progression FU

Patients who discontinue study treatment for any reason other than disease progression as per irRC will be followed up for progression of disease (Section 7.1.5). The disease progression follow-up will be performed until all patients enrolled in the Phase II part of the study have had progression of disease or discontinued the study for any reason.

Survival FU

Patients enrolled in Phase Ib and Phase II part will be followed for survival (Section 7.1.5) until the end of the study is reached, unless patients withdraw consent or are lost to follow-up.

4.2 Timing of interim analyses and design adaptations

No formal interim analyses are planned in the study. However, in the Phase Ib part, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. In the Phase II part the number of patients with tumor response will be monitored in each disease group to decide if the enrollment should be extended (see Section 2.2, Section 4.1 and Section 10.7). The decision of whether to expand a certain group will be made at the time when at least 3 patients, for Group 1or 3, or at least 2 patients for Group 4 have an objective response (CR or PR) per RECIST v1.1 or irRC, or the last patient has been on treatment for at least 6 months, whichever occurs earlier. For Group 2, the decision to expand will be made if clinical benefit per RECIST v1.1 or irRC (CR, PR or SD > 4 months) is observed in at least 3 patients or the last patient has been on treatment for at least 6 months. The decision to extend enrolment will be made separately for each of the groups.

4.3 Definition of end of the study

The end of the study will be when:

- 80% of the patients have completed the survival follow-up period (minimum 18 months after the first dose of treatment) or discontinued the study for any reason, and all patients have completed treatment and the safety follow-up period (150 days after last PDR001 dose or 90 days for patients who stopped PDR001 and continued with MCS110 alone for more than 60 days),

or

- the study is terminated early

or

- another clinical study becomes available that can continue to provide study treatment in this patient population, all patients ongoing are transferred to that clinical study and all discontinued patients have completed the safety follow-up period. The follow-up for disease progression and survival will not be performed or pursued (see Section 7.1.5).

At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative treatment option to patients who, in the opinion of the investigator, are still deriving clinical benefit.

4.4 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 for End of Treatment (EOT) visit and the assessments for EOT should be performed as described in Section 7.1.3 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 Institutional Review Boards (IRBs) and/or independent ethics committees (IECs) of the early termination of the trial.

5 Population

5.1 Patient population

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:

1. Written informed consent must be obtained prior to any procedures
2. Age ≥ 18 years [For Japan only: written consent is necessary both from the patient and his/her legal representative if he/she is under the age of 20 years.]
3. Phase Ib part: Patients with advanced melanoma, endometrial carcinoma, pancreatic or TNBC, with measurable or non-measurable disease as determined by RECIST v 1.1 (refer to Appendix 1), who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists.
4. Phase II part: Patients with advanced solid tumors, with at least one measurable lesion as determined by RECIST version 1.1, who have received standard therapy (no more than 3 prior lines of treatment) or are intolerant of standard therapy, have progressed following their last prior therapy, and fit into one of the following groups:
   - Group 1: TNBC who did not receive prior anti-PD-1/PD-L1 treatment

- Group 2: Pancreatic adenocarcinoma who did not receive prior anti-PD-1/PD-L1 treatment
- Group 3: Endometrial carcinoma who did not receive prior anti-PD-1/PD-L1 treatment
- Group 4: Melanoma who progressed on prior anti PD-1/ PD-L1-directed treatment.

5. ECOG performance status ≤ 2
6. Patient must have a site of disease amenable to biopsy, and be a candidate for tumor biopsy according to the treating institution's guidelines. Patient must be willing to undergo a new tumor biopsy at screening, and during therapy on this study. Patients with an available archival tumor tissue collected less than 6 months before study startup do not need to perform a tumor biopsy at screening.

5.3 Exclusion criteria

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

1. Presence of symptomatic CNS metastases, or CNS metastases that require local CNS-directed therapy (such as radiotherapy or surgery). Patients with treated brain metastases should be neurologically stable (for 4 weeks post treatment and prior to study enrollment) and off of steroids for at least 2 weeks before administration of any study drug.
2. History of severe hypersensitivity reactions to other monoclonal antibodies (mAbs).
3. Patient having out of range laboratory values defined as:
   - Creatinine clearance (calculated using Cockcroft-Gault formula, or measured) < 40 mL/min
   - Total bilirubin > 1.5 x ULN, except for patients with Gilbert's syndrome who are excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN
   - Alanine aminotransferase (ALT) > 3 x ULN
   - Aspartate aminotransferase (AST) > 3 x ULN
   - Absolute neutrophil count < 1.0 x 10^9/L
   - Platelet count < 100 x 10^9/L
   - Hemoglobin (Hgb) < 9 g/dL
4. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
   - Clinically significant and/or uncontrolled heart disease such as congestive heart failure requiring treatment (NYHA Grade ≥ 2), uncontrolled hypertension or clinically significant arrhythmia
   - QTcF > 470 msec on screening ECG or congenital long QT syndrome
   - Acute myocardial infarction or unstable angina pectoris < 3 months prior to study entry
5. Active autoimmune disease or a documented history of autoimmune disease within three years before screening, including the following:
   - A documented history of inflammatory bowel disease (ulcerative colitis or Crohn's disease, within three years).

- Recent (< 12 months) active diverticulitis.
- Patients with vitiligo, resolved childhood asthma/atopy and type I diabetes mellitus, residual hypothyroidism due to an autoimmune condition and only requiring hormone replacement, are not excluded.

6. Active infection, including active tuberculosis requiring systemic antibiotic therapy
7. Known human immunodeficiency virus (HIV) infection (no testing required).
8. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or HBV/HCV carriers/infections requiring antiviral treatment (testing required).
9. Malignant disease, other than that being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma *in situ* of any type.
10. Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures or interpretation of study results, including but not limited to:
    - Prior immune-related adverse events requiring treatment discontinuation
    - Ongoing symptomatic interstitial lung disease (ILD), noninfectious pneumonitis or history of drug induced interstitial lung disease
11. Systemic anti-cancer therapy within 2 weeks or 5 x T ½, whichever is longer of the first dose of study treatment. For cytotoxic agents that have major delayed toxicity, e.g. mitomycin C and nitrosoureas, 4 weeks is indicated as washout period. For patients receiving CTLA-4, PD-1 or PD-L1 antagonists, 6 weeks is indicated as the washout period.
12. Patients requiring chronic treatment with systemic steroid therapy or any immunosuppressive therapy, other than replacement-dose steroids in the setting of adrenal insufficiency. Any previous steroid or immunosuppressive therapy must be stopped at least 7 days before start of study treatment. Topical, inhaled, nasal and ophthalmic steroids are not prohibited.
13. Use of any live vaccines against infectious diseases (e.g. varicella, pneumococcus) within 4 weeks of initiation of study treatment.
14. Major surgery within 2 weeks of the first dose of study treatment (mediastinoscopy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery).
15. Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field. To allow evaluation for response to treatment, patients enrolled in the Phase II part must have remaining measurable disease that has not been irradiated.
16. Participation in an interventional, investigational study within 2 weeks of the first dose of study treatment.
17. Presence of ≥ CTCAE Grade 2 toxicity (except alopecia, peripheral neuropathy and ototoxicity, which are excluded if ≥ CTCAE Grade 3) due to prior cancer therapy.

18. Use of hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF) ≤ 2 weeks prior start or study drug. An erythroid stimulating agent is allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment.
19. Pregnant or 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.
20. 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 and for 150 days after the last dose of PDR001 or 90 days after the last dose of MCS110 for patients who stopped PDR001 and continued MCS110 alone for more than 60 days. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. 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 1.5 months 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 patients on the study the vasectomized male partner should be the sole partner for that patient.
    - 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 over 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile age appropriate (e.g. generally 40-59 years), history of vasomotor symptoms (e.g. hot flushes) in the absence of other medical justification or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at least 1.5 months 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.

21. For Korea only: Sexually active males unless they use a condom during intercourse while taking treatment and for 150 days after the last dose of PDR001 or 90 days after the last dose of MCS110 for patients who stopped PDR001 and continued MCS110 alone. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

6.1 Study treatment

For this study, the investigational drugs are MCS110, an anti-CSF-1 recombinant humanized monoclonal antibody, and PDR001, an anti-PD-1 receptor recombinant humanized monoclonal antibody. The study treatment is the combination of MCS110 and PDR001, or single agent MCS110 or PDR001 if one of the investigational drug need to be discontinued.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
MCS110	Liquid concentrate in vial i.v. infusion	3 mg/kg (starting dose)	Every 3 weeks
PDR001	Powder for solution for infusion	100 mg (starting dose)	Every 3 weeks

MCS110 and PDR001 will be administered once every 3 weeks via i.v. infusions over 1 hour and30 minutes, respectively. The drugs will be administered separately with at least a 30 min break between the two antibodies. Infusions of each antibody can be extended to up to 2 hours if clinically indicated.

Both study drugs may be infused using the same i.v. access site. The same administration sequence must be followed for all patients, i.e. PDR001 should be infused first. If an infusion reaction occurs after administration of PDR001, the subsequent MCS110 infusion must be delayed until it is safe for the patient to receive MCS110 based on the clinical discretion of the investigator. The delay between PDR001 and MCS110 infusions can be up to 4 hours if clinically indicated.

A scheduled dose of ongoing study drugs may be delayed by up to 7 days to recover from previous AEs or a missed visit (see Section 6.3.2). If a scheduled dose of ongoing study drugs is delayed longer than 7 days due to an unresolved AE, the administration should be skipped and treatment resumed at a lower dose level (if meeting criteria for DLT) at the next scheduled dose. The assessment schedule will be shifted accordingly. Dose delays refer to all ongoing study drugs: for combination treatment both MCS110 and PDR001 and for single agent treatment MCS110 or PDR001. Dose modifications should follow Section 6.3.1 and Section 6.3.2.

The dose for MCS110 study drug will be calculated from the individual subjects' body weight as measured at the screening visit and subsequent visits prior to the administration.

After Phase Ib part, if emerging PK, PD, and safety data indicate that a flat dosing strategy of MCS110 is appropriate, then a flat dosing strategy may be implemented in the Phase II part of the study. The PK data obtained during Phase Ib part of this study will be combined with PK data from the other MCS110 clinical studies to assess the flat dosing vs. body-weight based dosing, and a flat dose may be identified for the Phase II part of this study.

6.1.2 Ancillary treatments

Patients should not receive pre-medication to prevent infusion reactions before the first infusion of the study treatment, in order to determine if pre-medication is necessary. If a patient experiences an infusion reaction, he/she may receive pre-medication on subsequent dosing days. The pre-medication should be chosen per institutional standard of care at the discretion of the treating physician; however, steroids should be avoided if possible.

Acute allergic reactions should be treated as needed per institutional standard of care. In the event of anaphylactic/anaphylactoid reactions, this includes any therapy necessary to restore normal cardiopulmonary status. If a patient experiences a Grade 3 anaphylactic/anaphylactoid reaction, the patient may only continue on the study following discussion with Novartis.

Patients should be treated in a facility equipped for cardiopulmonary resuscitation. Appropriate resuscitation equipment should be available at the bedside and a physician readily available.

Guidelines on management of infusion reactions are provided in Table 6-4.

The CTCAE category of "Infusion related reaction" should be used to describe infusion reactions, unless the investigator considers another category, such as "Allergic reaction," "Anaphylaxis," or "Cytokine release syndrome" more appropriate in a specific situation.

6.1.3 Treatment duration

A patient may continue to receive study treatment until the patient experiences unacceptable toxicity, confirmed disease progression per irRC and/or treatment is discontinued at the discretion of the investigator or the patient. Patients will not be withdrawn from the study due to progressive disease per RECIST. In addition to safety and efficacy criteria, investigator's opinion of the patients best interest and clinical benefit from treatment may be discussed on a case by case basis with Novartis. Refer to Section 6.3.1, Section 7.1.4 and Section 7.1.6.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

This is the first study evaluating the combination of MCS110 and PDR001. Potential overlapping toxicities include liver enzyme elevations caused by immune induction (PDR001) or reduced elimination of liver enzymes (MCS110), higher frequency or aggravation of immune mediated adverse events and skin toxicity.

The starting dose and regimen of MCS110 will be 3 mg/kg iv every 3 weeks, corresponding to approximately 40 % of the single agent dose administered in PVNS patients (10 mg/kg every 4 weeks in study [MCS110X2201]) and 30 % of the dose administered in combination with carboplatin/gemcitabine in TNBC (10 mg/kg every 3 weeks in study [MCS110Z2201]). An MCS110 dose of 10mg/kg was well tolerated in HV and PVNS patients ([CMCS110X2101] and [CMCS110X2201]) and showed significant tumor reduction in PVNS patients. After a single dose of 3 mg/kg of MCS110 in HV, it was observed that CSF-1 has been saturated by MCS110 for approximately 21 days [CMCS110X2101]. PD analyses performed in HV studies indicate that circulating biomarker response should be close to maximal with dose at or above 5mg/kg and minimal with doses below 3 mg/kg. Considering the risk of potential overlapping

toxicities, the dose of 3 mg/kg MCS110 was selected as the starting dose for the dose escalation part of the study.

The starting dose and regimen of PDR001 will be 100 mg iv every 3 weeks. As of 30-Nov-2015, PDR001 has been tested up to the dose of 10 mg/kg every 2 weeks in the ongoing [CPDR001X2101] study. No MTD has been determined and the planned RP2D is 300 mg (3.75 mg/kg) given every 3 weeks or 400 mg (5 mg/kg) given every 4 weeks. Both of the proposed RP2Ds would be expected to achieve the steady mean C_{trough} concentrations that are approximately 77 fold higher than the in vitro/ex vivo potency EC50 for PDR001 assessed as 0.42 µg/mL. In addition, the expected PDR001 C_{trough} concentrations are in line with observed steady state mean C_{trough} concentrations for pembrolizumab whose ex vivo potency EC50 is approximately 0.4 µg/mL utilizing the same assay. Pembrolizumab has been approved with substantial efficacy in several cancer types. The PDR001 exposure at a starting dose of 100 mg Q3W is within the range of those observed in the CPDR001X2101 study with no DLTs (section 1.2.1.2). PDR001 is expected to demonstrate antitumor activity at doses of 100 mg or above every 3 weeks.The starting dose is in accordance with clinical experience of nivolumab and pembrolizumab (Topalian 2012, Topalian 2014, Hamid 2013b, Robert 2014).

6.2.2 Provisional dose levels

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-2 Provisional dose levels

Dose level *	Proposed dose MCS110	Proposed dose PDR001
-2**	0.3 mg/kg Q3W	100 mg Q3W
-1**	1 mg/kg Q3W	100 mg Q3W
1 (starting dose)	3 mg/kg Q3W	100 mg Q3W
2	3 mg/kg Q3W	300 mg Q3W
3	5 mg/kg Q3W	300 mg Q3W
4	10 mg/kg Q3W	300 mg Q3W

* It is possible for additional and/or intermediate dose levels to be added during the course of the study. Cohorts may be added at any dose level below the MTD in order to better understand safety, PK or PD

** Dose level -1 or -2 represent provisional dose levels and/or treatment doses for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -2 is permitted for this study

6.2.3 Guidelines for dose escalation and determination of MTD or RP2D

The maximum tolerated dose (MTD) is defined as the highest combination drug that is unlikely (< 25% posterior probability) to cause DLT in 33% or more of the treated patients in the **first two cycles (42 days)** of treatment.

The applied adaptive Bayesian methodology provides an estimate of the combinations of MCS110 and PDR001 not exceeding the MTD. Typically the MTD is a tested combination with maximum probability of targeted toxicity (DLT rate between 16% and < 33%). The use of the EWOC principle limits the risk that a potential next dose will exceed the MTD (Section 10.4.2). Adverse events and laboratory abnormalities considered to be DLTs are defined in Table 6-3.

For the purposes of dose escalation decisions, each cohort will consist of 3 to 6 newly enrolled patients who will be treated at the specified dose level. The first cohort will be treated with the starting doses of 3 mg/kg MCS110 Q3W and 100 mg PDR001 Q3W.

Patients must complete a minimum of two cycles of treatment with the minimum safety evaluation and drug exposure or have had a DLT within the first two cycles of treatment to be considered evaluable for dose escalation decisions (Section 10.1.4). Dose escalation decisions will occur when the cohort of patients has met these criteria. If only 2 of the 3 patients in a cohort are evaluable and neither subject has experienced a treatment-related toxicity > CTCAE Grade 1, dose escalation decisions may be considered.

Dose escalation decisions will be made by Investigators and Novartis study personnel. Decisions will be based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs, all CTCAE Grade ≥ 2 toxicity data during Cycle 1 and 2, PK, and PD data from evaluable patients. The recommended dose for the next cohort of subjects will be guided by the BLRM with EWOC principle evaluating the probability of DLT (Section 10.4.2)

The adaptive Bayesian methodology provides an estimate of all dose levels of the combination MCS110/PDR001 that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation. In general, the next dose will have the highest chance that the DLT rate will fall in the target interval [16-33%) and will always satisfy the EWOC principle (less than 25% probability that the DLT rate is ≥ 33%). In all cases, the dose for the next cohort will not exceed a 100% increase from the previous dose (except for the first dose escalation step where MCS110 remains at 3 mg/kg, while PDR001 is allowed to have a 200% increase from 100 mg). Smaller increases in dose may be recommended by the Investigators and Sponsor upon consideration of all of the available clinical data.

If 2 patients in a previously untested dose level experience a DLT, enrollment to that cohort will stop, the BLRM will be updated and the next cohort will be opened at the next lower dose level or an intermediate dose level (see Table 6-2 for provisional dose levels and Appendix 3) that satisfies the EWOC criteria. However, if 2 patients in a new cohort at a previously tested dose level experience a DLT (e.g., a total of 8 patients are treated on this dose level with 2 DLTs observed), further enrollment to that cohort will stop, the BLRM will be updated with this new information and re-evaluation of the available safety, PK, and PD data will occur. By incorporating information gained at the preceding dose cohorts, additional patients may be enrolled into the current dose level or a lower dose level as agreed by Investigators and Novartis personnel and if the BLRM predicts that the risk for this dose to exceed the MTD(s) remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports this EWOC criteria are satisfied and Investigators and Novartis personnel agree

Dose escalation will continue until identification of the RP2D which is expected to occur before the MTD is reached. This will occur when the following conditions are met:

1. at least 6 patients have been treated at this dose
2. this dose satisfies one of the following conditions:
    a. the posterior probability of targeted toxicity at this dose exceeds 50% and is the highest among potential doses, or

b. minimum of 15 patients have already been treated on the trial to identify the MTD. Recommendation of RP2D may be made with fewer patients, without identification of MTD.

3. it is the dose recommended for patients, either per the model or by review of all clinical data by Novartis and Investigators in a dose-escalation teleconference, see Section 6.2.3.1.

To better understand the safety, tolerability and PK of both MCS110 and PDR001, additional cohorts of patients may be enrolled at preceding dose levels, or to intermediate dose levels before or while proceeding with further dose escalation.

If a decision is made to escalate to a higher dose level but one or more additional patient(s) treated at the preceding dose level experiences a DLT during the first two cycles of treatment, then the BLRM will be updated with this new information before any additional patients are enrolled at that higher dose level. Subjects ongoing will continue treatment at their assigned dose levels.

6.2.3.1 Implementation of Dose Escalation Decisions

To implement dose escalation decisions, the available toxicity information (including all safety data, AEs Grade ≥ 2 and laboratory abnormalities that are not DLTs), the assessment of those doses satisfying the EWOC criterion from the BLRM, and the available PK and PD information will all be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) during a dose decision meeting by teleconference. All occurrences of DLT will be discussed and agreed at the dose decision teleconference among participating investigators and Novartis study personnel.

Cohort enrollment and drug administration at the next higher dose level may not proceed until the investigator receives written confirmation from Novartis indicating that the results of the previous dose level were evaluated and that it is permissible to proceed to a higher dose level with written confirmation of the next higher dose level to be tested.

6.2.3.2 Intra-Patient dose escalation

Intra-patient dose escalation is not permitted at any time within the first 6 months of treatment. After the 6 months of treatment is completed, individual patients may be considered for treatment at doses of MCS110 and PDR001 in combination higher than the doses to which they were initially assigned. Only one of the study drugs will be escalated at any one time. Study drugs will be escalated as detailed in Section 6.2.2. In order for a patient to be treated at a higher treatment dose, he or she must have tolerated the lower dose of MCS110 and PDR001 combination for at least two cycles of therapy (e.g., he or she must not have experienced a toxicity of CTCAE Grade ≥ 2 at the lower dose pair for which relationship to study drug cannot be ruled out). Moreover, the new, higher dose pair with which the patient is to be treated must be a dose pair that has completed evaluation in a dose-escalation meeting and that has satisfied the EWOC criterion under the Bayesian model.

There is no limit to the number of times a patient may have his or her treatment dose increased. Any further increases after the initial intra-patient dose escalation are subject to the same rules as for the initial intra-patient escalation. Consultation with Novartis must occur prior to any

intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record CRF.

6.2.4 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value of CTCAE Grade ≥ 3 assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first two cycles of treatment with the combination treatment and meets any of the criteria included in Table 6-3.

Emerging data from the new field of immune-immune combination studies suggest that some immune-related adverse events have a prolonged latency (Wolchok 2013). As such, the DLT window for the combination cohort in this trial is extended to the length of two cycles or 42 days.

National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE) version 4.03 will be used for all grading. For the purpose of dose-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the Sponsor immediately of any unexpected CTCAE Grade ≥ 3 adverse events or laboratory abnormalities. Prior to enrolling patients into a higher dose level, CTCAE Grade ≥ 2 adverse events will be reviewed for all patients at the current dose level.

DLTs include any adverse event of CTCAE Grade 3 or higher occurring in the first two cycles of treatment during the Phase Ib dose escalation part of the study, for which relationship to study treatment cannot be ruled, with the exceptions defined in Table 6-3.

Table 6-3 Criteria for defining dose-limiting toxicities

For the purpose of dose escalation and cohort expansion, DLT will be defined as follows: **Any Grade 4 AEs will be considered DLTs with the exception of:**	
	Neutropenia lasting ≤ 5 days that is not associated with fever or other clinical symptoms.
	Lymphopenia or leukopenia at any grade
Any Grade 3 AEs will be considered DLTs with the exception of:	
	Electrolyte abnormalities that are not associated with clinical sequelae and are corrected to ≤ Gr1 with appropriate management or supplementation within 72 hours of onset.
	Infusion reaction that resolves to ≤ Grade 1 within 6 hours.
	Nausea and vomiting persisting for < 2 days with optimal anti-emetic therapy.
	Thrombocytopenia without significant bleeding.
	Diarrhea persisting for < 2 days with optimal anti-diarrhea therapy.
	Hypertension persisting < 7 days with optimal therapy.
	Infection or fever in the absence of neutropenia persisting < 7 days.
	Rash or photosensitivity persisting < 7 days after treatment.
	Fatigue lasting < 7 days.
	Immune-related adverse events persisting at Grade3 < 7 days after treatment with corticosteroids.
	*CK elevation without associated muscle damage per investigator discretion
	*Isolated AST elevations (without bilirubin or ALT elevations ≥ Grade 1)
The following Grade 2 AEs will be considered as DLTs:	
	Total bilirubin > 2 x ULN with ≥ CTCAE Grade 2 AST/ALT.

	Pneumonitis persisting > 7 days despite treatment with corticosteroids.
	Eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment.
	Other clinically significant toxicities, including a single event or multiple occurrences of the same event may be considered as DLT's.
* MCS110 treatment results in CK and AST elevations without any association to muscle damage (Radi 2011). The CK/AST elevations are caused by reduced clearance rate from the circulation due to the diminished numbers of macrophages (Kupffer cells) in the liver (Section 1.2.2.1).	

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment, except during the first two cycles when dose modifications are only allowed if the patient experiences a DLT. The following guidelines need to be applied:

- If a patient experiences an AE meeting the criteria for DLT as outlined in Section 6.2.4, treatment should be withheld. Dose modifications for toxicities related to the study medication are summarized in Table 6-4. Following resolution of the toxicity to Grade 1 or to the patient's baseline value, the patient may resume study treatment at a lower dose level than is being tested at that time (on the same dosing schedule), if there is no evidence of disease progression as per irRC. A decision to resume treatment following the occurrence of a DLT is at the discretion of the Investigator. Following an AE meeting criteria for DLT, if a patient resumes study treatment, it should be at the next lower dose level. Dose reductions to doses below MCS110 0.3mg/kg / PDR001 100 mg Q3W are not permitted. If more than 2 consecutive doses have to be skipped due to study treatment-related toxicities, then the patient must be discontinued from the study unless the patient experiences clinical benefit in the opinion of the investigator. In this case, treatment can be continued at a dose agreed by Novartis and the investigator.
- For clinical management of suspected immune-related events, reference to consensus management guidelines is recommended such as those provided in the National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immunotherapy-Related Toxicities (available at : https//wwwnccn.org/professionals/physician_gls/default.aspx#immunotherapy), the American Society for Clinical Oncology clinical practice guideline for Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy (Brahmer 2018) or the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines for Management of Toxicities from Immunotherapy (Haanen 2017). Note that in general, study treatment should be interrupted for grade 3 and 4 toxicities and for a subset of lower grade toxicities.
- Consider early referral to specialists with expertise in the diagnosis and management of immune-related AEs to thoroughly investigate events of uncertain etiology.
- Events not included in the study protocol or the reference guidance documents should be managed per institutional preference.

- If one of the study drugs is discontinued the patient may continue with the remaining study drug, if the investigator considers it to be in the patient's best interest. The dose of the remaining study drug must be agreed by Novartis and the investigator.

Patients who discontinue the study treatment for a study related AE or a study-related abnormal laboratory value must be followed as described in Section 6.3.2.

Table 6-4 Dose modification for drug related toxicities

Toxicity	Dose Adjustment Rules*
Hematology	
Neutropenia (ANC)	
Grade 3 or Grade 4.	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor
Febrile neutropenia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution of fever and improvement of neutropenia to ≤ Grade 2 or baseline, resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Thrombocytopenia	
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline, resume study treatment without dose modification. For Grade 3 associated with major bleeding, discontinue study treatment.
Grade 4	Discontinue study treatment.
Anemia	
Grade 3 or Grade 4	Hold study treatment. Upon resolution to ≤ Grade 2 or baseline within ≤ 7 days, resume study treatment without dose modification.
Lymphopenia	
Any grade	Treatment-related lymphopenia does not require study treatment hold or discontinuation.
Gastrointestinal	
Diarrhea/colitis*	
Grade 1	May continue study treatment without dose modification. Manage per institutional standard guidelines which should include anti-diarrheal treatment, consideration of corticosteroid therapy, and hydration.
Grade 2	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, resume study treatment without dose modification after discussion with the Novartis Medical Monitor.
Grade 3	Hold study treatment. GI consultation. Upon resolution to ≤ Grade 1 and tapering of steroid requirement to ≤ 10 mg prednisone per day, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade4	Discontinue study treatment.

Toxicity	Dose Adjustment Rules*
Hepatic (AST and/or ALT elevation)	
Grade 2 AST and/or ALT	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1 or baseline, consider resuming study treatment without dose modification.
Grade 2 transaminitis with bilirubin >1.5 x ULN (unless Gilbert's syndrome)	Discontinue study treatment.
Grade 3 AST and/or ALT	Hold study treatment. Manage per institutional practices. Upon resolution to ≤ Grade 1 or baseline within 7 days, consider resuming study treatment without dose modification after discussion with the Novartis Medical Monitor. Otherwise, discontinue study treatment
Grade 4 AST and/or ALT	Discontinue study treatment.
Isolated total bilirubin elevation**	
Grade 2	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may continue study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1 or baseline, may consider resuming study treatment after discussion with the Novartis Medical Monitor.
Grade 4	See footnote**. Otherwise, discontinue study treatment.
Asymptomatic amylase and/or lipase elevation***	
Grade 3 or Grade 4, not associated with symptoms or clinical manifestations of pancreatitis***	Continue study treatment. If levels do not resolve to ≤ Grade 2 within ≤ 14 days after the initial report, hold study treatment. Upon resolution to ≤ Grade 2, may resume study treatment without dose modification, after discussion with the Novartis Medical Monitor.
Pancreatitis	
Grade 2 / radiologic evidence	Hold study treatment. Manage per institutional practice. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification, if no clinical evidence of pancreatitis and after discussion with the Novartis Medical Monitor.
Grade 3-4	Discontinue from treatment.
CK elevation	
Grade 3-4	Monitor CK-MB isoenzyme, troponin (I or T), and creatinine. ● If CK-MB and troponin (I or T) are normal, creatinine ≤ 1.5 x baseline and patient asymptomatic, continue treatment. ● If CK-MB and troponin (I or T) are abnormal or creatinine (> 1.5 x baseline and > ULN) or patient symptomatic, delay treatment 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, restart treatment. Decrease MCS110 1 dose level.
Cytokine Release Syndrome (CRS)	
Grade 2	See instructions for Grade 2 Infusion Reaction.

Toxicity	Dose Adjustment Rules*
Grade 3 and Grade 4	Discontinue study treatment. Follow-up CRS as per institutional guidelines. Take blood for cytokine measurements as specified in Section 7.2.2.5.5 Laboratory evaluations.
Renal (creatinine)	
Grade 2	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management..
Grade 3 or 4	Discontinue study treatment.
Endocrine	
Hypothyroidism or hyperthyroidism	
Grade 2	May continue study treatment without dose modification. Management according to institutional practice.
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	May resume therapy following resolution or control with physiologic hormone replacement.
Other endocrine disorders	
Grade 2 and Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 with appropriate management, may resume study treatment without dose modification.
Grade 4	Hold study treatment. Grade 4 treatment-related endocrinopathies, such as adrenal insufficiency, adrenocorticotropic hormone (ACTH) deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Novartis Medical Monitor.
Pulmonary (pneumonitis)	
Grade 1	Consider study treatment hold. Manage per institutional practice. Consider resuming study treatment upon radiographic evidence of improvement.
Grade 2	Hold study treatment. Pulmonary and infection workup. Upon resolution to ≤ Grade 1, may resume study treatment without dose modification
Grade 3 or 4	Discontinue study treatment.
Ocular (uveitis)	
Grade 1	Continue study treatment without dose modification. Ophthalmology consultation.
Grade 2	Hold study treatment. Urgent ophthalmology consultation. Upon resolution to ≤ Grade 1 may consider resuming study treatment without dose reduction after discussion with the Novartis Medical Monitor and in consultation with ophthalmology

Toxicity	Dose Adjustment Rules*
Grade 3 or 4	Discontinue from treatment. Urgent ophthalmology consultation.
Periorbital edema	
Grade 2	Delay treatment until resolved to ≤ Grade 1. Decrease MCS110 1 dose level.
Grade 3-4	Discontinue from treatment.
Dermatology (rash)	
Grade 1	Continue study treatment without dose modification. Topical steroids, antihistamines, topical emollients
Grade 2	Consider holding study treatment. Topical or oral steroids, antihistamines. If study treatment is held and resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3 or Grade 4	Hold study treatment. Manage per institutional practice. After resolution to ≤ Grade 1, consider resuming study treatment after discussion with the Novartis Medical Monitor.
Bullous dermatitis	Hold study treatment. Grade 1-2 bullous dermatitis: discussion with the Novartis Medical Monitor is required before considering resuming study treatment. Grade 3 bullous dermatitis: consider resuming therapy after expert consultation and documented discussion with the Novartis medical monitor. Grade 4 bullous dermatitis: discontinue study treatment.
Stevens-Johnson syndrome (SJS), or Lyell syndrome/toxic epidermal necrolysis (TEN)	Permanently discontinue study treatment.
Cardiovascular	
ECG QTc-Interval prolonged; hypertension	
Grade 3	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline (hypertension, QTc) or < 30 msec difference from baseline (QTc) within ≤ 7 days, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor. Baseline ECG refers to the ECG(s) collected at screening
Grade 4	Discontinue study treatment
Other cardiovascular disorders	
Grade 2 (except myocarditis)	Hold study treatment. Upon resolution to Grade ≤ 1 or baseline, may resume study treatment without dose modification after discussion with the Novartis Medical Monitor..
Grade 2 myocarditis, or Grade ≥ 3 other cardiac disorders related to study treatment	Discontinue study treatment
Musculoskeletal	
Grade 2 or Grade 3	Hold study treatment. Consider resuming study treatment without dose modification upon resolution to ≤ Grade 1 with appropriate management.
Grade 4	Discontinue study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor and consultation with a rheumatologist.

Toxicity	Dose Adjustment Rules*
Neurology	
Grade 1	Consider study treatment hold, particularly for clinical suspicion of Guillain-Barre syndrome, encephalitis, aseptic meningitis, transverse myelitis, or peripheral neuropathy.
Grade 2	Hold study treatment. In some cases, resuming study treatment may be considered after discussion with the Novartis Medical Monitor.
Grade 3 or Grade 4	Discontinue study treatment.
Infusion Reaction	
Grade 1	Decrease infusion rate until recovery
Grade 2	Stop infusion. Before restarting - administer oral pre-medication (e.g.1000 mg of acetaminophen/paracetamol, 50-100 mg diphenhydramine hydrochloride or alternative antihistamine), within 60 minutes of restarting the infusion. Restart infusion at 50% of previous rate under continuous observation. Ensure that there is a minimum observation period of 1 hour prior to restarting the infusion(s). If the AE recurs at the reinitiated slow rate of infusion, and despite oral pre-medication, then discontinue patient from treatment.
Grade 3 or 4	Discontinue infusion immediately, and discontinue study treatment. Provide supplemental oxygen, fluids, and other resuscitative measures as needed. Monitor vital signs (e.g. blood pressure, pulse, respiration, and temperature) every 15 ± 5 minutes until resolution.
Other laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 4	Isolated Grade 4 electrolyte abnormalities not associated with clinical sequelae and corrected after appropriate management within 72 hours of their onset do not require discontinuation. In the case of Grade 4 electrolyte imbalances associated with clinical sequelae, or not resolved to ≤ Grade 1 within 72 hours despite appropriate management, discontinue study treatment.
Other non-laboratory adverse events, not specified elsewhere in table and not included in the consensus guidelines	
Grade 2	Consider study treatment hold, at Investigator discretion. Upon resolution to ≤ Grade 1, resume study treatment without dose modification.
Grade 3	Hold study treatment. Upon resolution to ≤ Grade 1, resuming study treatment must be discussed with the Novartis Medical Monitor.
Grade 4	Discontinue from treatment.

*Delay: treatment may be delayed for 7 days due to AEs. If a scheduled dose of ongoing study drugs is delayed longer than 7 days due to an unresolved AE, the administration should be skipped and treatment resumed at a lower dose level (if meeting the criteria for DLT) at the next scheduled dose (Section 6.1.1).
Treatment: refers to both study drugs, unless one has been discontinued.

Toxicity	Dose Adjustment Rules*
**Note: If Grade 3 or 4 hyper-bilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then delay study treatment until resolved ≤ Grade 1, and resume study treatment at the discretion of the investigator.	
***Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within one week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase.	

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value, must be followed-up at least once a week (or more if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts should be consulted as deemed necessary. Consensus management algorithms for immune-related AEs have been developed and are available to assist investigators in assessing and managing immune-related AEs (refer to Section 6.3.1). In case of a toxicity suspected to be a cytokine release syndrome, the assessments outlined in Section 7.2.2.5.5 must be performed.

All patients must be followed up for AEs and SAEs for 150 days after the last dose of PDR001 or 90 days after the last dose of MCS110 for patients who stopped PDR001 and continued MCS110 alone for more than 60 days.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced immune related adverse events, are provided in Table 6-4. The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures as well as, close clinical monitoring. There may be unforeseen risks with MCS110 in combination with PDR001 which could be serious. Refer to preclinical toxicity and or clinical data found in the MCS110 and PDR001 Investigator's Brochure.

6.4 Concomitant medications

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.

6.4.1 Permitted concomitant therapy requiring caution and/or action

Therapeutic treatment with hematopoietic colony-stimulating growth factors G-CSF or GM-CSF may only be initiated after the first two cycles in the dose escalation part of the study, unless the patient has already experienced a DLT. If available GM-CSF is preferred over G-CSF (Eyles 2006).

Treatment with erythroid stimulating agents may not be initiated during the first two cycles in the dose escalation part of the study, unless the patient has already experienced a DLT. If a patient is using an erythroid stimulating agents prior to enrollment (at least 2 weeks before start of study treatment), they may continue at the same dose.

Anticoagulants are permitted if the patient is already at stable doses of warfarin or taking stable doses of low molecular weight heparin for >2 weeks at time of first dose and INR should be monitored as clinically indicated per investigator's discretion. However, ongoing anticoagulant therapy should be temporarily discontinued to allow tumor biopsy according to the institutional guidelines.

Anti-hypertensives are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, consideration should be given to withholding anti-hypertensive medications for 12 hours prior to infusion with MCS110 and PDR001.

Statins should be used with caution since CK elevations are commonly seen and transient CK elevations were noted in healthy volunteers and patients studies with MCS110.

6.4.2 Prohibited concomitant therapy

During the course of the study, patients may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study.

Prophylactic treatment with hematopoietic colony-stimulating growth factor G-CSF or GM-CSF is prohibited since it may induce immune suppression and promote tumor growth (Eyles 2006).

The use of systemic steroid therapy and other immunosuppressive drugs is not allowed, with the only exclusion of steroids for the treatment infusion reaction, irAEs or replacement-dose steroids in the setting of adrenal insufficiency. Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at doses ≤ 10 mg/day of prednisone or equivalent before the next study drug administration. Systemic steroid therapy required during the course of the study to manage other concurrent medical conditions should be discussed with Novartis.

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

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first pre-screened (if applicable) or when the patient is enrolled for screening. The subject number 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 informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition page.

6.5.2 Treatment assignment or randomization

The assignment of a patient to a particular cohort will be coordinated by the sponsor. No randomization will be performed in this study.

6.6 Study drug preparation and dispensation

PDR001 (100 mg powder for solution for infusion) will be administered first as a 30 minute intravenous infusion (up to 2 hour, if clinically indicated). MCS110 (7.5ml of 20 mg/ml concentrate in vial) will be administered intravenously as an 1 hour infusion (up to 2 hour, if clinically indicated). At least 30 min break should occur between the two infusions.

Further instructions for the preparation and dispensation of MCS110 and PDR001 are described in the [Pharmacy Manual].

All dosages prescribed to the patient, all dose interruptions and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

6.6.1 Study drug packaging and labeling

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

PDR001 100 mg powder for solution for infusion will be supplied as open label bulk medication.

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.

6.6.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the

instructions specified on the drug labels and in the MCS110 and PDR001 Investigator's Brochure.

6.6.3 Study drug compliance and accountability

6.6.3.1 Study drug compliance

Study treatment 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.

6.6.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. 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 log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

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

No CRF will be used as a source document.

Screening/baseline evaluations must be performed ≤ 21 days before Cycle 1 Day 1, except for baseline radiological evaluations which must be done within 28 days. Assessments performed as part of the screening evaluations and within 3 days prior to the first dose of study treatment, are not required to be repeated on the first dosing day.

Laboratory and radiological assessments performed as part of standard of care prior to signing informed consent may be used if performed within 21 days and 28 days respectively, of Cycle 1 Day 1.

During the course of the study visits, test and/or procedures should occur on schedule whenever possible. A visit window of ± 7 days is allowed. If the infusion of MCS110 and/or PDR001 is delayed, the visits assessments will be shifted accordingly. On PK collection days the windows are provided in Section 7.2.3.

Radiological assessments must be performed ± 1 week of the scheduled date of the assessment.

For Japan only, patients are required to be hospitalized during Cycle 1.

Table 7-1 Visit evaluation schedule

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**	**Cycle 4**					**Subsequent cycles**	**EOT**	**Safety F/U**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**1**	**2**	**4**	**8**	**15**	**1**				
Obtain Informed Consent	D	7.1.1	X																		
Demography	D	7.1.1.2	X																		
Inclusion/ exclusion criteria	D	5.2 and 5.3	X																		
Medical History	D	7.1.1.2	X																		
Diagnosis and extent of cancer	D	7.1.1.2	X																		
ER, PR, HER2, BRCA1 and BRCA2 status (TNBC)	D	7.1.1.2	X																		
Prior antineoplastic therapy	D	7.1.1.2	X																		

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**	**Cycle 4**					**Subsequent cycles**	**EOT**	**Safety F/U**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**1**	**2**	**4**	**8**	**15**	**1**				
Prior/concomitant medications, surgery and medical procedures	D	7.1.1.2 7.1.5 and 6.4	X	Continuous[1]																	
Physical examination	S	7.2.2.1	X	X			X	X	X	X	X	X					X	X			
Height	D	7.2.2.3	X																		
Weight	D	7.2.2.3	X	X					X		X	X					X	X			
Vital signs	D	7.2.2.2	X	X			X	X	X	X	X	X					X	X			
Performance status	D	7.2.2.4	X	X					X		X	X					X	X			
Hematology	D	7.2.2.5.1	X	X			X	X	X	X	X	X			X		X	X			
Chemistry	D	7.2.2.5.2	X	X			X	X	X	X	X	X			X		X	X			
Coagulation	D	7.2.2.5.6	X	Only if clinically significant														X			
Urinalysis	D	7.2.2.5.3	X	X					X		X	X					X	X			
Thyroid function	D	7.2.2.5.4	X	X					X		X	X					X	X			
Cytokines (E.g. IFN-γ; IL-6, IL-1, TNFα)	D	7.2.2.5.5		X	In case of cytokine release syndrome																
Pregnancy test	D	7.2.2.5.7	X						X		X	X					X	X	X[2]		

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**	**Cycle 4**					**Subsequent cycles**	**EOT**	**Safety F/U**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**1**	**2**	**4**	**8**	**15**	**1**				
Virology	D	7.2.2.5.8	X																		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5																	X	X^{7}	X^{7}
Tumor evaluation as per RECIST v1.1 and as per irRC.	D	7.2.1	X	Every 2 cycles from Cycle 3 Day 1 up to Cycle 9 Day 1 (C3D1, C5D1, C7D1, C9D1), then every 3 cycles until Cycle 18 Day 1 (C12D1, C15D1 C18D1). Assessment will be performed every 4 cycles thereafter, starting from Cycle 22 Day 1. For disease progression f/u, every 9 weeks ± 1 week until week 51 after study start, then every 12 weeks± 1 week until progression of disease per irRC, withdrawal of consent, or lost to follow-up.															
Tumor markers	D	7.2.1	X	X																	
12-leads ECG	D	7.2.2.6.1	X	X								X						X			
Chest x-ray [for Japan only]	D	7.2.2.7	X				X														
Adverse events	D	8	Continuous																		
[redacted]																					
Study drug administration	D	6.1.1		i.v. every 3 weeks for MCS110 and PDR001																	
PK sampling	D	7.2.3		X	X^{4}	X^{4}	X	X^{4}	X		X	X	X^{4}	X^{4}	X	X^{4}	X^{5}				

			Screening Phase	Treatment Phase														Follow-up		
Visit name	**Category**	**Protocol Section**	**Screening**	**Cycle 1**					**Cycle 2**		**Cycle 3**	**Cycle 4**					**Subsequent cycles**	**EOT**	**Safety F/U**	**Disease Progression F/U**	**Survival F/U**
Day of cycle			**-21 to -1**	**1**	**2**	**4**	**8**	**15**	**1**	**15**	**1**	**1**	**2**	**4**	**8**	**15**	**1**				
Immunogenicity (IG) sampling	D	7.2.3		X					X		X	X					X[5]				
[redacted]																					
Survival contact	D	7.1.5																			X

[1] Concomitant medications are only collected until 30 day of follow-up or the start of antineoplastic therapy, whichever comes first.
[2] Urine pregnancy test should be performed every month during and at the end of 150 days safety follow-up (90 days in case patient is only taking MCS110 alone, for more than 60 days).
[redacted]
[4] Day 2, 4, 15 sampling times are only applicable to the Phase Ib part,
[5] Cycles 5 and 6 only,
[6] Only on C5D1
[7] In reference to Section 7.1.5, the follow-up for safety, disease progression and survival will not be performed for patients who transfer to another clinical study to continue provision of study treatment or an alternative treatment option. For all other patients, the safety evaluation period will be completed but the disease-progression and survival follow up will not be performed.

7.1.1 Screening

The study IRB/IEC approved informed consent form must be signed and dated before any screening procedures are performed, except for laboratory and radiological evaluations performed as part of standard of care within the screening window.

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 window (Section 7.1).

7.1.1.1 Information to be collected on screening failures

A patient who signed an Informed Consent Form but failed to be started on treatment for any reason will be considered a screen failure.

The screening failure 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 patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during screening (see Section 8.2 for SAE reporting details).

7.1.1.2 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 cancer, details of prior anti-neoplastic treatments, prior medication, procedures, significant non-drug therapies and any other assessments that are done for the purpose of determining eligibility for inclusion in the study.

For patients with breast cancer, ER, PR and HER2 status will be collected. In addition BRCA1 and BRCA2 genotype must be collected.

7.1.2 Treatment period

A treatment cycle is defined as 21 days for the purposes of scheduling procedures and evaluations. 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 they experience unacceptable toxicity, progressive disease per irRC and/or treatment is discontinued at the discretion of the investigator or the patient, as described in Section 7.1.3 and Section 4.3.

Patients should not discontinue treatment based on progressive disease per RECIST v1.1.

Accumulating evidence indicates that objective responses to immunotherapy follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or appearance of new lesions or some enlarging lesions while other target lesions are regressing (“mixed response”) (Wolchok 2009). It is therefore reasonable to allow for these possibilities and continue to treat the patient until progression is confirmed and found to be advancing at the next imaging assessment as per irRC. An outline of the irRC is provided in Appendix 2.

These considerations should be balanced by clinical judgment as to whether the patient is clinically deteriorating and unlikely to receive any benefit from continued treatment.

Such deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the patient is not benefiting from study treatment and cannot be managed by the addition of supportive care.

The decision to continue or stop treatment should be discussed with the Novartis Medical Responsible and will be documented in the study files.

The following criteria should be considered for treatment continuation decision making:

- Patients with partial response or stable disease as well as patients with unconfirmed progressive disease (per irRC) should continue to receive study treatment until the next cycle.
- Patients with confirmed irPD will discontinue study drug(s) and enter the Follow-up period (see Section 7.1.5). Patients who have either a poor performance status or toxicity requiring both MCS110 and PDR001 discontinuation and do not have a confirmed irPD will enter the Follow-up period until confirmed irPD, initiation of a new treatment, completion of all Follow-up visits. Patients will then enter the Survival Follow-up period.
- Patients with confirmed PD/irPD in stable or improved clinical status can remain under treatment, after discussion with Novartis, until there is a further progression or clinical deterioration under the following circumstances:
  - Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression;
  - No decline in ECOG performance status;
  - Absence of rapid progression of disease;
  - Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

7.1.3 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
- Physician's decision
- Progressive disease per irRC (not per RECIST v1.1)

- Study terminated by Novartis
- Subject/guardian decision
- Protocol deviation

Study treatment must be discontinued in case of 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 treatment 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 7.1.5. 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 7.1.6. If a patient discontinues study treatment, but continues study assessments, the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the Study Phase Completion Disposition CRF page.

Patients who transfer into another study to continue provision of study treatment or an alternative treatment option will perform the end of treatment procedures.

7.1.3.1 Replacement policy

Phase Ib dose escalation part:

Patients will not be replaced on study. However, if a patient is considered as non-evaluable for dose determination and cannot be part of the Dose Determination Set (DDS), enrollment of a new patient to the current cohort will be considered if there is less than the required number of evaluable subjects. Enrollment of new subjects may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable subjects is achieved within the cohort. Minimum and maximum numbers of evaluable subjects per cohort are defined in Section 6.2.3.

Phase II part:

During the Phase II dose expansion part no replacements will be needed.

7.1.4 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 anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the patient's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

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

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

7.1.5 Follow-up period

Safety Follow-up

All patients must have safety evaluations until 150 days after the last dose of PDR001 or 90 days after the last dose of MCS110 (whichever the longer). The 30-, 90- and 150-day safety follow-up can be done by telephone call or visit.

Concomitant medications will be collected until the 30-day safety follow-up has been completed or the start of a new antineoplastic therapy, whichever occurs first.

Data collected should be added to the Adverse Events CRF, the antineoplastic therapies since discontinuation of study treatment CRF, and the Concomitant Medications CRF.

For a female participant of child bearing potential, a pregnancy test will be performed on a monthly basis after stopping the study treatment (Section 7.2.2.5.7).

For patients who transfer to another clinical study to continue provision of study treatment or an alternative treatment option, as described in Section 4.3, the follow-up for safety will not be performed. For all other patients, the safety evaluation period will be completed but the disease-progression and survival follow up will not be performed.

Disease progression follow-up period

Patients who discontinue study treatment for any reason other than death, disease progression per irRC, lost to follow-up, consent withdrawal, start of new cancer therapy or study

termination, should return for tumor evaluation assessments every 9 weeks until 51 weeks, then every 12 weeks until progression of disease per irRC, withdrawal of consent, lost to follow-up (Section 7.2.1), or until the end of the study is reached as described in Section 4.3.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine if the patient had disease progression.

For patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for disease progression will not be performed.

Survival follow-up period

Upon completion of the safety follow-up and disease progression follow-up (if applicable), all patients enrolled in the Phase Ib and Phase II parts will be followed for survival every 3 months (can be done by telephone call) until death or until the end of the study is reached, as described in Section 4.3, unless they withdraw consent or are lost to follow-up.

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

For patients who transfer to another clinical study or an alternative treatment option to continue provision of study treatment, the follow-up for survival will not be performed.

7.1.6 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 two sets of criteria:

1. RECIST v1.1 (Appendix 1)
2. irRC (Appendix 2)

The local investigator's assessment will be used for the analysis of response according to both RECIST v1.1 and irRC, and for treatment decision making (study discontinuation due to PD is per irRC). During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed.

At screening, all patients will undergo CT with i.v. contrast of the chest, abdomen and pelvis. If there is clinical evidence of disease in the neck, a CT with i.v. contrast of the neck will also

be performed. MRI should only be used to evaluate sites of disease that are not adequately imaged by CT. If a patient is intolerant of iodine-based contrast agents, CTs may be performed without contrast. 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. See Table 7-2 for further details.

Tumor assessments will be performed at the following time points until progression of disease per irRC or patient withdrawal:

- Screening
- Every 2 cycles from Cycle 3 Day 1 up to Cycle 9 Day 1, then every 3 cycles until Cycle18 Day 1 (1 year of treatment). Assessment will be performed every 4 cycles thereafter, starting from Cycle 22 Day1.
- At the End of Treatment, if a scan was not conducted within 30 days prior to End of Treatment
- After EOT, during disease progression follow-up, every 9 weeks (± 1 week) until week 51, then every 12 weeks (± 1 week), until progression of disease per irRC.
- PR or CR, per both RECIST v1.1 and irRC, will be confirmed by a new assessment after at least 4 weeks. Also Progressive Disease (PD), as per irRC, will be confirmed after at least 4 weeks.

If available, tumor markers collected as per local guidelines will be collected at the same time as RECIST tumor evaluation.

Efficacy assessments should be performed ± 1 week from the calculated study day as described in Section 7.1. Disease progression follow-up should be performed as described in Section 7.1.5.

Table 7-2 Disease assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT or MRI (with intravenous contrast enhancement)	Mandated	● Every 6 weeks until end of cycle 8 (C3D1, C5D1, C7D1, C9D1) ● Thereafter every 9 weeks (C12D1, C15D1, C18D1). ● During year two, assessment can be performed every 4 cycles, starting from C22D1. ● End of treatment, if not conducted within 30 days prior to EOT.
Tumor markers	If available as per local guideline	Same time as CTor MRI tumor assessment, if available as per local guideline
Brain CT or MRI	If clinically indicated	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis
Localized bone CT, MRI or x-ray of other metastatic sites (eg neck or bone)	For any lesions already identified that are not visible on the chest, abdomen and pelvis CT or MRI	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

Procedure	Screening/Baseline	During Treatment/Follow-up
Color photography (with scale/ruler)	For any skin lesions present	If lesions were documented at baseline, follow same schedule as CT/MRI of chest, abdomen, and pelvis

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, hematology, chemistry, thyroid function, pregnancy, ECG, as well as collecting the AEs at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

Physical examination will be performed according to Table 7-1.

At Screening and Cycle 1 Day 1, prior to treatment administration, a complete physical examination will be performed and will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

From Cycle 1 Day 8 onwards, a short physical examination will be performed. A short physical exam will include the examination of general appearance, vital signs (body temperature, blood pressure [BP] and pulse) and body sites as directed by symptoms.

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

[For Japan only: oxygen saturation (SpO2) will be measured by pulse oximetry for Japanese patients every time physical examination is performed as indicated in Table 7-1.]

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed before dosing and as indicated in Table 7-1.

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 if medically indicated, and will be recorded as unscheduled assessment.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured as indicated in Table 7-1.

7.2.2.4 Performance status

ECOG performance status will be assessed according to Table 7-1 and Table 7-3.

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 selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

7.2.2.5 Laboratory evaluations

Abnormal laboratory values that are clinically significant (e.g., require an interruption or delay of study treatment, lead to clinical symptoms, or require therapeutic intervention) must be documented in the Adverse Event eCRF.

Novartis will be provided with a copy of the site's local laboratory certification and tabulation of the normal ranges for each parameter required at study start and should be kept up to date on an ongoing basis. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges for that laboratory.

Table 7-4 Local/Central Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, White blood cells with differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils,)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Bicarbonate, Calcium, Phosphate, Chloride, Magnesium, Creatinine, Glucose (non fasting), Creatine kinase, Lactate dehydrogenase (LDH), Total Bilirubin (also measure direct and indirect bilirubin if total bilirubin is > Grade 1), Blood Urea Nitrogen (BUN) or Urea, Uric Acid. CK-MB isoenzyme, Troponin I/T, Aldolase or Myoglobin or other skeletal muscle marker- if required per local guidelines to rule out myositis/rhabdomyolysis (see Section 7.2.2.6.2)
Cytokines *	IFN-γ, IL-6, IL-1,TNF-α
Urinalysis	Macroscopic panel (Dipstick) (Bilirubin, Blood, Glucose, Ketones, White blood cells, pH, Protein, Specific Gravity) Myoglobin-if required to rule out myositis/rhabdomyolysis per local guidelines
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Thyroid	T3 [free], T4 [free], TSH
Virology	HBV and HCV
*To be performed by a Central Laboratory	

7.2.2.5.1 Hematology

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

7.2.2.5.2 Clinical chemistry

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

7.2.2.5.3 Urine analysis

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

7.2.2.5.4 Thyroid function

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

7.2.2.5.5 Cytokines

Samples for the cytokine panel outlined in Table 7-4 will be collected at the following time points:

- Baseline (predose C1D1)
- On an *ad-hoc* basis, in case a patient has an adverse event suspected to be a cytokine release syndrome. In such case, this assessment should be performed at the following time points:
  a. within 5 hours (or as soon as possible) after the occurrence of the adverse event
  b. one week after the occurrence of the adverse event.

Samples for cytokine panel assessment will be stored locally below -70°C. The samples will be analyzed retrospectively in batches by the Novartis designated central laboratory. Immediate analysis of the samples by the central lab will be done only for patients who experienced an adverse event suspected to be a cytokine release syndrome and had follow-up samples collected.

7.2.2.5.6 Coagulation

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

7.2.2.5.7 Pregnancy

Pregnancy tests will be performed for women of child bearing potential per Table 7-1.

At screening, a serum pregnancy test must be performed within 3 days before the first dose. During the study (Day 1 of each Cycle starting with Cycle 2), and at the End of Treatment visit, a serum pregnancy test must also be performed.

A urine pregnancy test should be performed every month during and at the end of the safety follow-up period (i.e. 150 days after the last dose of PDR001 or 90 days after the last dose of MCS110 for patients who stopped PDR001 and continued MCS110 alone for more than 60 days). If the patient is not coming to the clinic during the safety follow-up, it can be performed at home or at a local doctor's office, and the results will be communicated to the site staff. These follow-up pregnancy tests will be recorded only in the source documentation, not in the CRF.

7.2.2.5.8 Virology

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

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. Blood samples scheduled at the same time point should be taken after the ECGs are completed. The ECGs on C1D1, and C4D1 must be performed in triplicate. For the Screening, EOT and Unscheduled visits only one ECG per visit is required.

Table 7-5 Local ECG collection plan

Cycle	Day	Time
Screening	-21 to -1	Anytime
1	1	*Pre-dose (0 hr)
1	1	*1hr (±5 min) hour post last treatment administration
4	1	*Pre-dose
4	1	*1hr (±5 min) hour post last treatment administration
EOT	-	Anytime
Unscheduled**	-	Anytime
* ECGs performed in triplicate at these PK matched timepoints only. ** A PK sample should be collected just after an ECG was performed due to an unexpected cardiac signal.		

Interpretation of the tracing must be made by a qualified physician and documented on the ECG CRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the Medical History CRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events CRF page.

7.2.2.6.2 Cardiac and skeletal muscle markers.

Due to known asymptomatic creatine kinase elevations associated with MCS110, additional labs will be analyzed to rule out cardiac muscle damage (CK-MB and Troponin I/T) or skeletal muscle damage (aldolase, myoglobin or other skeletal muscle marker per local guidelines). The muscle damage markers will be measured at baseline and anytime during the study in case of CK elevation ≥5 x ULN.

7.2.2.7 [For Japan only] Radiological examinations

7.2.2.7.1 Chest x-ray

A 2-view chest x-ray will be performed at screening and Day 8 of Cycle 1.

7.2.3 Pharmacokinetics and immunogenicity assessments

PK profiles to assess PK properties of MCS110 and PDR001 will be collected from all enrolled patients. However, only the patients from Phase Ib part will have additional PK collected on day 2, 4 and 15.

Immunogenicity (IG) samples will also be collected to monitor appearance of anti-drug antibodies directed against MCS110 or PDR001. Please refer to Table 7-6 and Table 7-7 for details on PK and IG sample collections.

If the dosing of Cycle 4 Day 1 is delayed, the PK sampling for the full PK profile should be delayed accordingly to match the scheduled time points for Cycle 4 as outlined in Table 7-6 and Table 7-7. After the primary CSR data cut-off date is reached, no additional PK and IG samples will be collected for the patients still on-going on the study.

[redacted]

Table 7-6 Phase Ib Part: Pharmacokinetic blood collection log for MCS110, PDR001 and IG samples

Cycle	Study day	Analytes	Scheduled time point (Sampling window)	Total volume of Blood sample
1	1	MCS110, PDR001 and IG [a]	Pre-dose [b] (0 hr)	6 mL
1	1	MCS110, PDR001	1 hr (± 5 min) post end of C1D1 infusion dose [c]	4 mL
1	2	MCS110, PDR001	24 hr (± 2 hr) post dose	4 mL
1	4	MCS110, PDR001	72 hr(± 6 hr) post dose	4 mL
1	8	MCS110, PDR001	168 hr (± 8 hr) post dose	4 mL
1	15	MCS110, PDR001	336 hr (± 8 hr) post dose	4 mL
2	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 2 (0 hr)	6 mL
3	1	MCS110, PDR001 and IG [a]	Pre-dosed [b] of cycle 3 (0 hr)	6 mL
4	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 4 (0 hr)	6 mL
4	1	MCS110, PDR001	1 hr (± 5 min) post end of C4D1 infusion dose [c]	4 mL
4	2	MCS110, PDR001	24 hr (± 2 hr) post dose of cycle 4	4 mL
4	4	MCS110, PDR001	72 hr (± 6 hr) post dose of cycle 4	4 mL
4	8	MCS110, PDR001	168 hr (± 8 hr) post dose of cycle 4	4 mL
4	15	MCS110, PDR001	336 hr (± 8 hr) post dose of cycle 4	4 mL
5	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 5 (0 hr)	6 mL
6	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 6 (0 hr)	6 mL
EOT		MCS110, PDR001 and IG [a]		6 mL

Cycle	Study day	Analytes	Scheduled time point (Sampling window)	Total volume of Blood sample
Blood samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline. [a] Immunogenicity (IG) (Anti-Drug [MCS110 or PDR001] Antibody): blood samples to be collected for anti-drug antibody together with PK samples [b] Pre-dose blood samples should be collected prior to start of infusion of any treatment [c] MCS110 sampling time is relative to the end of MCS110 infusion; PDR001 sampling time is relative to the end of PDR001 infusion				

Table 7-7 Phase II Part: Pharmacokinetic blood collection log for MCS110, PDR001 and IG samples

Cycle	Study day	Analytes	Scheduled time point (Sampling window)	Total volume of Blood sample
1	1	MCS110, PDR001 and IG [a]	Pre-dose [b] (0 hr)	6 mL
1	1	MCS110, PDR001	1 hr (± 5 min) post end of C1D1 infusion dose [c]	4 mL
1	8	MCS110, PDR001	168 hr (± 8 hr) post dose	4 mL
2	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 2 (0 hr)	6 mL
3	1	MCS110, PDR001 and IG [a]	Pre-dosed [b] of cycle 3 (0 hr)	6 mL
4	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 4 (0 hr)	6 mL
4	1	MCS110, PDR001	1 hr (± 5 min) post end of C4D1 infusion dose [c]	4 mL
4	8	MCS110, PDR001	168 hr (± 8 hr) post dose of cycle 4	4 mL
5	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 5 (0 hr)	6 mL
6	1	MCS110, PDR001 and IG [a]	Pre-dose [b] of cycle 6 (0 hr)	6 mL
Blood samples are to be collected from the arm opposite from infusion site, or alternatively, infusion site will need to be flushed with 10 mL of saline. [a] Immunogenicity (IG) (Anti-Drug [MCS110 or PDR001] Antibody): blood samples to be collected for anti-drug antibody together with PK samples [b] Pre-dose blood samples should be collected prior to start of infusion of any treatment [c] MCS110 sampling time is relative to the end of MCS110 infusion; PDR001 sampling time is relative to the end of PDR001 infusion				

7.2.3.1 Analytical method

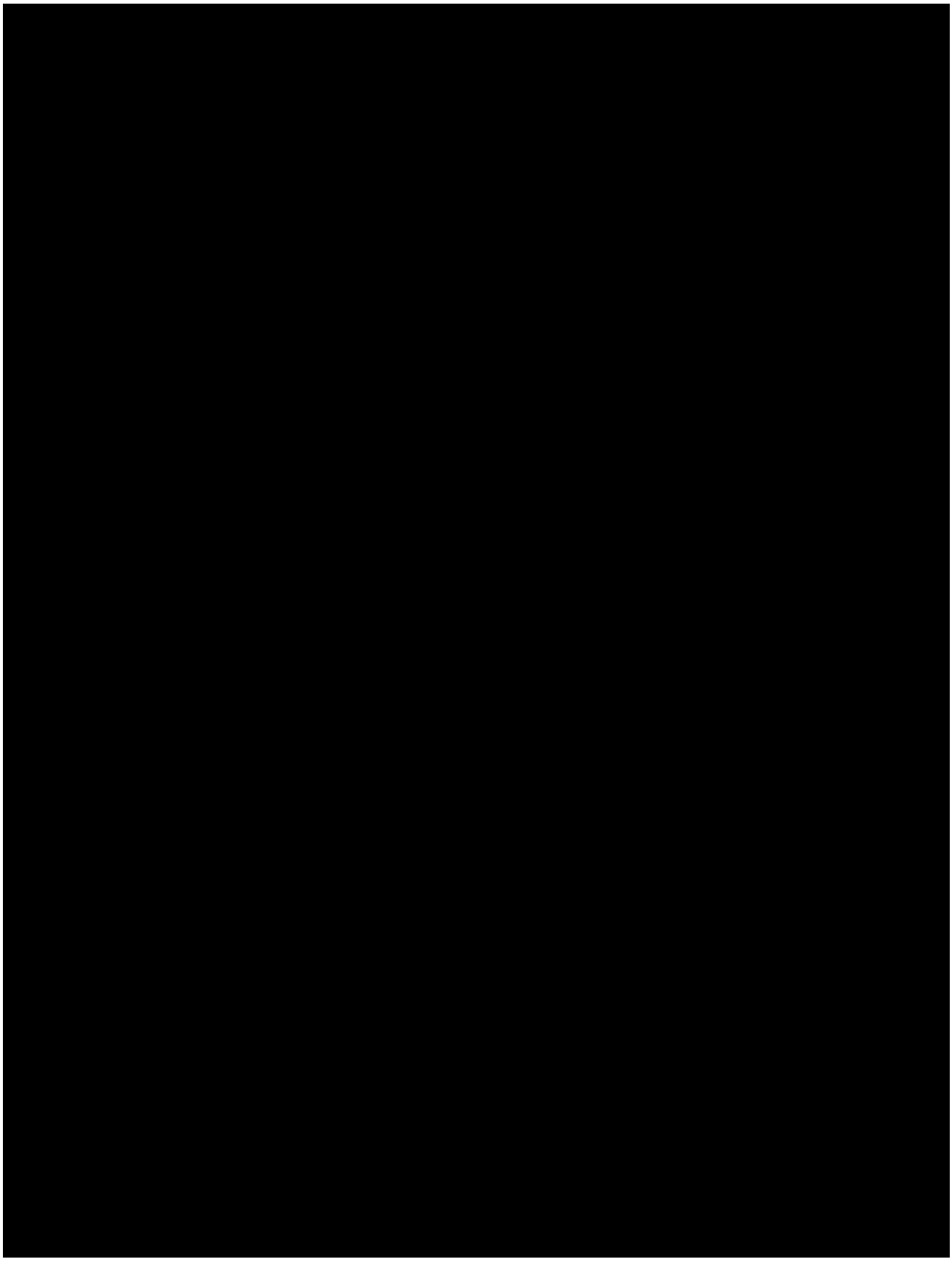
Bioanalysis for pharmacokinetic samples will employ the following validated assays:

1. The assay to quantify MCS110 will be a validated ELISA assay.
2. The assay to quantify PDR001 will be a validated LCMS assay.
3. The assay to quantify and assess the anti-MCS110 antibody will be a validated homogeneous ELISA.
4. The assay to quantify and assess the anti-PDR001 antibody will be a validated homogeneous ELISA.

7.2.3.2 PK and immunogenicity sample handling, labeling, and shipping instructions

A total of 4 mLs of blood will be collected at each time point for MCS110 and PDR001 PK. After clotting and centrifugation, the resulting serum will be separated into 6 aliquots (3 for MCS110 and 3 for PDR001) and will be stored frozen until analysis. For time points when MCS110 and PDR001 PK and IG for both molecules are to be measured, a total of 6 mLs of blood will be collected at each time point. The samples will be prepared as serum and will be aliquoted into 12 aliquots (3 aliquots for each analyte MCS110 PK, PDR001 PK, MCS110 IG and PDR001 IG). Blood samples should be collected from the arm opposite from the investigational drug infusion, or from another site. Please see the [Laboratory Manual] for detailed instructions about collection, handling and shipment of samples.

The actual collection date and time of each sample will be entered on the Pharmacokinetics/Immunogenicity Blood Collection eCRF pages.



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. 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 150 days after the last dose of PDR001 or 90 days after the last dose of MCS110 for patients who stopped PDR001 and continued MCS110 alone for more than 60 days).

After initiation of new post-treatment antineoplastic therapy, only AEs suspected to be related to study treatment will be collected in the Adverse Events CRF.

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 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 through 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:

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
- 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 irRC or as per RECIST), 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 test abnormalities

8.1.2.1 Definitions 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 or

irRC. 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 150 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence (90 days for patients who stopped PDR001 and continued MCS110 alone for more than 60 days).

If a patient starts a post treatment antineoplastic therapy, then only SAEs suspected to be related to study treatment will be reported.

Any SAEs experienced after this follow-up period 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 [For Japan only: complete the SAE report form in English or Japanese], 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. 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. After the mother has provided consent, the newborn will be followed-up for 12 months.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis CMO&PS department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

For Korea only: Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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 Data Monitoring Committee

A formal data monitoring board will not be used for this study. This is an open-label, Phase Ib/II study in which patients will receive MCS110 in combination with PDR001. Novartis will have access to the Safety Data on a regular basis. Novartis will host investigator teleconferences on a regular basis during the study. Further, during the Phase Ib part of the study, Novartis and the investigators will meet at the end of each treatment cohort to discuss and evaluate all of the gathered safety data. At the dose escalation teleconference the clinical course (safety information including both DLTs and all CTCAE Grade 2 or higher toxicity data during the first two cycles of treatment, and PK data) for each patient in the current dose cohort will be described in detail. Updated safety data on other ongoing patients, including data in later cycles, will be discussed as well.

Dose escalation decisions will be based on a clinical synthesis of all relevant available data and not solely on DLT information. Selection of the actual dose for the next cohort of patients will be guided by the BLRM with EWOC and a medical review of relevant clinical, PK and laboratory data. Novartis and the investigator parties must reach a consensus on whether to declare MTD, escalate the dose any further, or whether to de-escalate and/or recruit an additional cohort of patients at the current dose level (Section 10.4.2).

During the Phase II part of the study individual patient data will be reviewed on an ongoing basis. Overall response rate (ORR) for Group 1, 3, 4 and clinical benefit rate (CBR) for Group 2 per RECIST v1.1 and irRC and aggregate safety data will be monitored quarterly by the study team across the duration of the trial. Enrollment of each of Group 1, 3 and 4 will be expanded up to approximately 40 patients when objective responses (CR or PR) per RECIST v1.1 or irRC are observed (≥ 3 of 20 patients in each of the PD-1/PD-L1 therapy naïve groups or ≥ 2 of 20 patients in the PD-1/PD-L1 therapy resistant group). In Group 2, enrollment may be expanded up to approximately 40 patients at RP2D if clinical benefit per RECIST v1.1 or irRC (CR, PR or SD > 4 months) is observed in at least 3 pts. In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criteria is met (Group 2b). The decision of whether to expand a certain expansion group will be made at the time when the required number of responses is observed, or the last patient (out of 20 patients) has been on treatment for 6 months, whichever occurs earlier. The data review and analysis will be based on the available investigator reported data in the clinical database at that time Section 10.7.

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 [redacted] samples obtained during the course of the study will be collected from the Investigator sites and analyzed by a Novartis designated laboratory and/or contracted central laboratories. ECG data collected during the study will be reviewed locally by a cardiologist. During the course of the study, Novartis may decide to have a central review of the radiological assessments performed. In such case, the investigator's staff will be instructed on how to send data from these radiological assessments to a Contract Research Organization (CRO) for central review when needed. Designated investigational site

staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Field monitors will review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by the field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

For studies using eCRFs, Novartis personnel 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 are 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 Reference List, 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.

Samples and/or data will be processed centrally and the results will be sent electronically to Novartis.

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.

10 Statistical methods and data analysis

The data will be analyzed by Novartis and/or designated CRO. Any data analysis carried out independently by the investigator must be submitted to Novartis before publication or presentation.

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

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

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

- Phase Ib dose escalation data: cohorts treated during the dose escalation with the same dose levels of MCS110 and PDR001 will be pooled into a single treatment group. All summaries, listings, figures and analyses will be performed by treatment group.

- Phase II data: All summaries, listings, figures for non-safety analysis will be reported by group. Safety analysis of Phase II will be reported by group and all patients. For Group 2, all summaries, listings, figures will be reported by dose level, when applicable. The groups are the following:
  - Group 1: TNBC (naive to PD-1/PD-L1 directed therapy)
  - Group 2: Pancreatic cancer (naive to PD-1/PD-L1 directed therapy)
  - Group 3: Endometrial cancer (naive to PD-1/PD-L1 directed therapy)
  - Group 4: Melanoma (resistant to PD-1/PD-L1 directed therapy)

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

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

10.1 Analysis sets

10.1.1 Full Analysis Set

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

10.1.2 Safety Set

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

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

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

10.1.3 Per-Protocol Set

The Per Protocol Set (PPS) consists of a subset of FAS patients in the Phase II part who meet the following criteria:

- Presence of at least one measurable lesion according to RECIST v1.1 as per Appendix 1
- Have at least one post-baseline tumor assessment evaluable per RECIST v1.1, or have withdrawn due to clinical progression.
- Have received the planned treatment
- Have not been previously treated with PD-1 or PD-L1-directed therapy except patients in the melanoma pretreated group (Group 4), who must have previously received a PD-1 or PD-L1-directed therapy.

Patients will be classified according to planned treatment.

The PPS will be used in the Phase II part of the study only and will define the patients used in the sensitivity analysis of the primary endpoint Section 10.4. If the PPS and the FAS are identical, then analyses described by the PPS below will not be performed.

10.1.4 Dose-determining analysis set

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

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

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

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

10.1.5 Pharmacokinetic analysis set

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

- Subject receives the planned treatment
- Subject provides at least one primary PK parameter

Note: patients will be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of the analyses

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be listed in detail.

Qualitative data (e.g. performance status) and quantitative data (e.g. weight) will be summarized by appropriate descriptive statistics for each treatment cohort in Phase Ib and for each group in Phase II.

10.3 Treatments (study treatment, concomitant therapies, compliance)

For each of MCS110 and PDR001, the actual dose and duration in days of treatment as well as the dose intensity (actual dose received/actual duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be listed and summarized by means of descriptive statistics by treatment group. Categories for relative dose intensity of MCS110 or PDR001 will be specified as < 0.5, ≥ 0.5 - < 0.75, ≥ 0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by ATC term and treatment group.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last dose of MCS110 and PDR001 (if applicable), duration of exposure to MCS110 and PDR001 (if applicable) and date of discontinuation for each patient.

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

10.4 Primary objective

Phase Ib

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

Phase II

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

10.4.1 Variable

Phase Ib

The primary variables of Phase Ib are:

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

Phase II

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

For pancreatic patients, the primary variable of Phase II is the Clinical Benefit Rate (CBR), defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) (with at least two assessments 4 weeks apart) or stable disease (SD) > 4 months based on local Investigator assessment, as defined in RECIST v1.1.

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 Phase Ib

10.4.2.1.1 Identification of a recommended dose

The dose escalation part of this study will be guided by a Bayesian analysis of first two cycles dose limiting toxicity (DLT) data for MCS110 and PDR001 in combination. The Bayesian analysis will be based on a model with three parts, representing:

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

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

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

Single agent toxicity is modelled using logistic regression for the probability of a patient experiencing a DLT against log-dose. The odds of a DLT are then calculated under no interaction for the two single agent toxicities, and interaction is accounted for by adjusting these odds with an additional model parameter (odds multiplier). Details of the model are given in (Appendix 3).

Assessment of patient risk

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

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

The escalation with overdose control (EWOC) principle

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

Prior distributions

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

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

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

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

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

For each of the single agent prior, an additional high toxic component is introduced to allow for a higher toxicity case. A full description of the application of the MAP approach to derive the prior distributions of the single agent MCS110 and PDR001 model parameters is given in (Appendix 3)

The prior distribution for the interaction parameter was based upon prior understanding of possible drug safety interactions (Section 1.3.3). This prior allows for the possibility of either synergistic or antagonistic interaction, and is fully described in (Appendix 3).

Starting dose

The starting dose is 3 mg/kg for MCS110, and 100 mg for PDR001 which will be administered every 3 weeks (see Section 6.2.1). For this dose the prior risk of excessive toxicity is 10.4%, which satisfies the EWOC criterion. A full assessment of the prior risk to patients is given in (Appendix 3). Before first patient first visit (FPFV), the BLRM will be updated with additional PDR001 single agent data (if available) to ensure the starting dose still satisfies EWOC.

Listing of DLTs

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

10.4.2.1.2 Safety analyses

Analyses set and grouping for the analyses

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

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

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

3. post-treatment period: from 31 days after date of last administration of study treatment

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

Adverse events (AEs)

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

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

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group.

Specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s), which is specified in case retrieval strategy (CRS). SEC will be specified in the statistical analysis plan (SAP) and finalized prior to database lock.

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

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, biochemistry and urinary laboratory tests:

- Frequency table for newly occurring on-treatment grades 3 or 4 (see below for details).
- Shift tables using CTCAE grades to compare baseline to the worst on-treatment value.
- Listing of all clinically relevant 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, [redacted] analyses may be specified in the SAP.

ECG

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

Vital signs

Definitions of notably abnormal results will be specified in the SAP.

- Listing of vital signs
- shift table baseline to worst on-treatment result

10.4.2.1.3 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized (Section 10.3).

10.4.2.2 Phase II

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

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

Groups 1, 3 and 4 will enroll approximately 20 patients, and may be extended to approximately 40 patients (if at least 3 patients have an objective response for Group 1 and 3; and if at least 2 patients have an objective response for Group 4). In Group 2, 20 patients will be enrolled at RP2D, and enrollment may be extended to approximately 40 patients if clinical benefit is observed in at least 3 pts. In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criterion is met (Group 2b). See timing of the decision-making in Section 4.2. The primary analysis will be performed when all patients have completed at least 6 cycles of treatment or discontinued prior to that time for any reason.

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

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

- b = 1.

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. See sample size estimation in Section 10.8.

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

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

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

Note that, for a sample size of n = 40, if the observed ORR is 30% then the posterior probability of true ORR greater than 20% is 93.0%.

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

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

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. See sample size estimation in Section 10.8.

If the lower MCS110 dose level is explored (Group 2b), a separate model with the same prior assumption will be used to estimate CBR.

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

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

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

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

Group 4

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

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

At primary analysis, this prior distribution will be updated with all the data available from the patients in the FAS. See sample size estimation in Section 10.8.

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

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

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

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

10.4.3 Handling of missing values/censoring/discontinuations

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

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

For the Phase II part, the primary analysis on ORR may be repeated using PPS. Additional exploratory and supportive analyses will be performed if appropriate as defined in the SAP.

10.5 Secondary objective

10.5.1 Key secondary objective

Not applicable.

10.5.2 Other secondary efficacy objectives

Tumor response will be determined per local investigators' assessment, according to RECIST v1.1 and irRC. Response related efficacy assessments will be defined and analyzed based on both RECIST v1.1 and irRC. For the purpose of this study, Clinical benefit rate (CBR) is defined as the proportion of patients with a best overall response of CR or PR , or an overall lesion response of SD which lasts for more than 4 months.

Secondary efficacy endpoints include:

- Phase Ib part: ORR, PFS, CBR, DOR and DCR per RECIST v1.1 and per immune related Response Criteria (irRC)
- Phase II part: (1) For Group 1, 3, 4, ORR per irRC, PFS, DOR, DCR, CBR per RECIST v1.1 and per irRC; (2) For Group 2, CBR per irRC, PFS, DOR, DCR, ORR per RECIST v1.1 and per irRC

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

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

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

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

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

Any additional analyses of efficacy endpoints will be described in the SAP.

10.5.3 Safety objectives

Another secondary objective is to further characterize the safety and tolerability of MCS110 in combination with PDR001 during Phase II part. Safety and tolerability analyses as described in Section 10.4.2.1.2 and Section 10.4.2.1.3 will be performed.

10.5.4 Pharmacokinetics

The pharmacokinetic parameters will be determined by profile using noncompartmental method(s) for both MCS110 and PDR001 as presented in Table 10-1, and PAS will be used in all pharmacokinetic data analysis and PK summary statistics.

Table 10-1 Pharmacokinetic Parameters to be analyzed

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)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid 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 plasma (volume x time-1)
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)
AR	Accumulation Ratio=Cmax (multiple Dose)/Cmax (single dose)

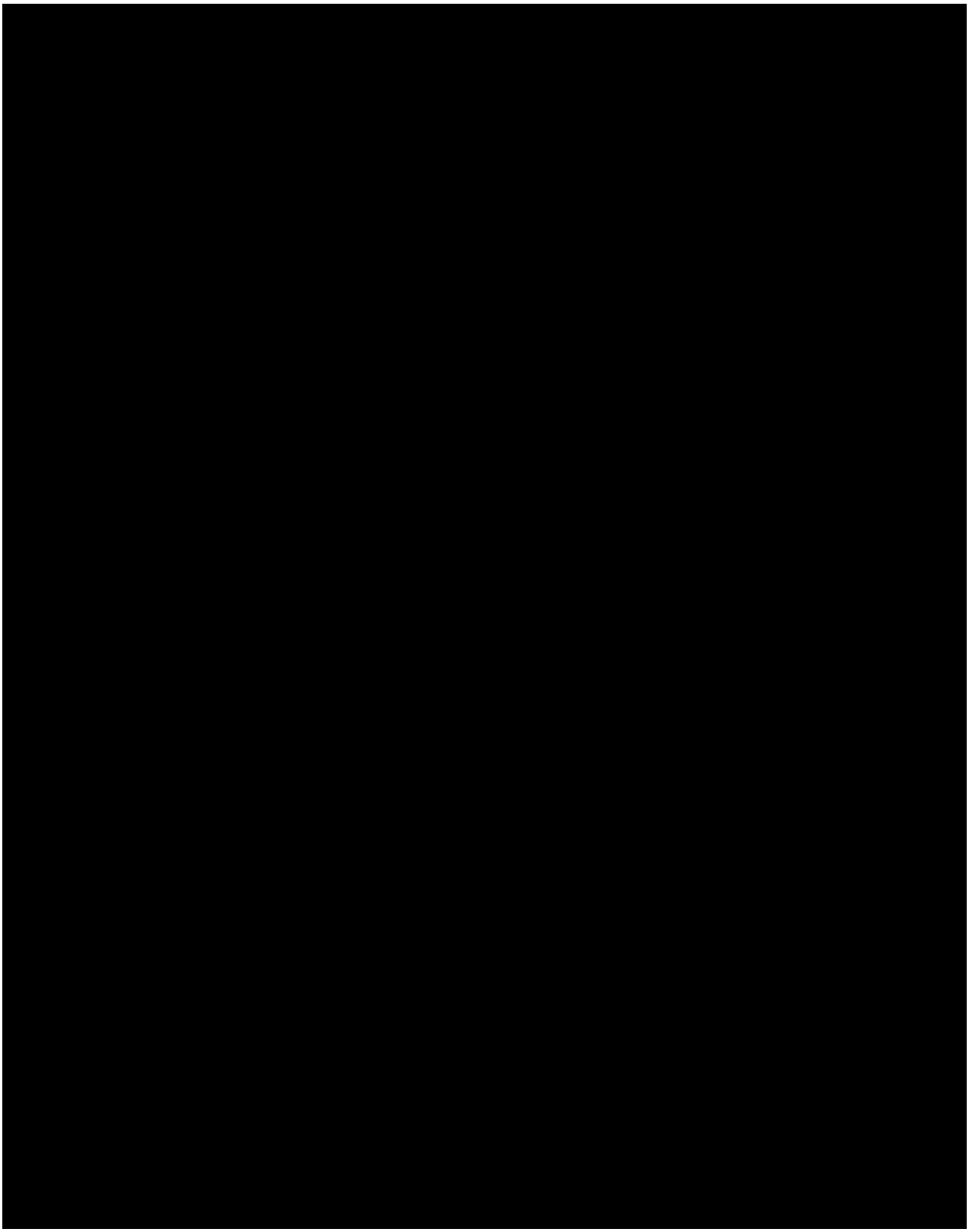
Descriptive statistics of all pharmacokinetic parameters will include arithmetic and geometric mean, median, SD, and CV, geometric CV, minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since Tmax is generally evaluated by a nonparametric method, median values and ranges will be given for this parameter.

Summary statistics will be presented for MCS110 and PDR001 serum concentrations at each scheduled time point. Descriptive graphical plots of individual serum concentration versus time profiles and mean concentration versus time profiles will be generated.

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

The presence of immunogenicity for MCS110 and PDR001, at each scheduled time point, will be listed by treatment group, disease and patient. Overall immunogenicity will be summarized.

More details will be provided in SAP or separate analysis plan.



10.7 Interim analysis

No formal interim analyses are planned.

Phase Ib

However, in Phase Ib, the dose-escalation design foresees that decisions based on the current data are taken before the end of the study. More precisely, after each cohort in the dose escalation part, the next dose will be chosen depending on the observed data (based on safety, tolerability, PK and PD, guided by the recommendations from the BLRM of DLT using EWOC, and recommendations from participating investigators). Details of this procedure and the process for communication with Investigators are provided in Section 6.2.3.

Phase II

Data from patients in the Phase II part will be reviewed on an ongoing basis to monitor the safety and tolerability of the RP2D in that part of the study. The sample size in any of Group 1, 3 or 4 may be extended to approximately 40 patients (if ≥ 3 of 20 patients in each of the PD-1/PD-L1 therapy naïve groups or ≥ 2 of 20 patients in the PD-1/PD-L1 therapy resistant group have tumor responses of CR or PR per RECIST v1.1 or irRC). In Group 2, 20 patients will be enrolled at RP2D, and enrolment may be expanded up to approximately 40 patients if at least 3 pts with CR, PR or SD > 4 months per RECIST v1.1 or irRC are observed. In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criterion is met (Group 2b). The decision of whether to expand a certain expansion group will be made at the time when the required number of responses is observed, or the last patient (out of 20 patients) has been on treatment for at least 6 months, whichever occurs earlier. The Investigators and Novartis will make the decision based on a synthesis of all relevant data available including safety, PK and PD information.

10.8 Sample size calculation

Phase Ib

Cohorts of 3 to 6 evaluable patients will be enrolled in the dose-escalation Phase including at least six patients at the MTD/RP2D level, as described in Section 6.2.3. Multiple cohorts may

be sequentially enrolled to the same dose level. Additional cohorts of 3 to 6 patients may be enrolled at any dose level below the estimated MTD/RP2D for further elaboration of safety and pharmacokinetic parameters as required. At least 15 patients are expected to be treated in the dose escalation Phase for the model to have reasonable operating characteristics relating to its estimation of MTD.

Phase II

Approximately 20 patients will initially be enrolled to each of groups 1, 3 and 4. Enrollment may be expanded up to approximately 40 patients in these groups if objective responses (CR or PR) per RECIST v1.1 or irRC are observed (≥ 3 of 20 patients in each of the PD-1/PD-L1 therapy naïve groups or ≥ 2 of 20 patients in the PD-1/PD-L1 therapy resistant group) (Section 2.2). In Group 2, 20 patients will be enrolled at RP2D, and enrolment may be expanded up to approximately 40 patients if at least 3 pts with CR, PR or SD > 4 months per RECIST v1.1 or irRC are observed. In addition, an exploratory group of 20 patients at a lower dose (1 mg/kg MCS110 in combination with PDR001 300 mg) may be opened if the above mentioned gating criterion is met (Group 2b). The operating characteristics of the designs are provided in Table 10-2 (for Group 1, 3), Table 10-3 (for Group 4), and Table 10-4 (for Group 2 at RP2D), Table 10-5 (for Group 2b).

Table 10-2 Operating characteristics of the design (Group 1, 3)

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

Table 10-3 Operating characteristics of the design (Group 4)

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

Table 10-4 Operating characteristics of the design (Group 2 at RP2D)

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

Table 10-5 Operating characteristics of the design (Group 2b)

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

10.9 Power for analysis of key secondary variables

Not applicable.

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.

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 4.4.

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. clinicaltrials.gov , before study start. In addition, results of interventional clinical trials in adult patients are posted on novartisclinicaltrials.com, a publicly accessible database of clinical study results within 1 year of study completion

(i.e., LPLV) and those for interventional clinical trials involving pediatric patients within 6 months of study completion.

Novartis follows the ICMJE authorship guidelines (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)

Harmonization of Efficacy Analysis of Solid Tumor Studies

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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
LPLV	Last patient last visit
MRI	Magnetic resonance imaging
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 14.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.1.3.2 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 14.1.4 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.

14.1.2.1 Definitions

14.1.2.1.1 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 14.1.3.2.8

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.

14.1.2.1.2 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 14.1.3.2.8.

14.1.2.2 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.

14.1.2.3 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 14.1.2.1.1.
- **Nodal target**: See Section 14.1.2.1.1.

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.

14.1.2.4 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.

14.1.2.4.1 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.

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.

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.

14.1.2.4.2 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 14.1.2.2

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.

14.1.2.4.3 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 14.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.1.2.4.4 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 14.1.2.5).
- 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 14.1.2.2.

14.1.2.5 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 14.1.2.4

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.

14.1.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.1.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

14.1.3.1 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 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).

14.1.3.2 Time to event variables

14.1.3.2.1 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.

14.1.3.2.2 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.

14.1.3.2.3 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.

14.1.3.2.4 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.

14.1.3.2.5 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.

14.1.3.2.6 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 14.1.3.2.5. 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.

14.1.3.2.7 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 14.1.3.2.8).

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.

14.1.3.2.8 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 14.1.2.4

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.

14.1.3.2.9 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 14.1.3.2.7, 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 14.1.3.2.7
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.3.2.7.
[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.

14.1.4 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).

14.1.4.1 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).

14.1.4.2 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 14 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
- Subject/guardian decision
- Death
- Progressive disease per irRC (not per RECIST)
- Study terminated by the sponsor

14.1.4.3 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

14.1.4.4 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.

14.1.4.5 Programming rules

The following should be used for programming of efficacy results:

14.1.4.5.1 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.

14.1.4.5.2 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 14.1.3.2.7). 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.

14.1.4.5.3 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.

14.1.4.5.4 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)'.

14.1.4.5.5 Study/project specific programming

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

14.1.4.5.6 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 (option
- Death due al, see Table 14-5) 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 14.1.3.2.7. 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.

14.1.5 References (available upon request)

Dent S, Zee (2001) application of a new multinomial phase II stopping rule using response and early progression, J Clin Oncol; 19: 785-791

Eisenhauer E, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). European Journal of Cancer, Vol.45: 228-47

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14.2 Appendix 2: Guidelines for immune-related Response Criteria (irRC) using one-dimensional measurements (simulating RECIST 1.1)

14.2.1 Introduction

The currently used immune-related response criteria (irRC) uses unidimensional measurements to assess tumor response and it is an adaptation of the original irRC published by Wolchok (Wolchok 2009, Nishino 2013).

The purpose of this document is to summarize the irRC guidelines in details focusing on differences in tumor response assessments between irRC and RECIST v1.1.

The primary difference between irRC and RECIST 1.1 is the definition of progressive disease. The definitions of baseline target/non target lesions, number of lesions selected at baseline, the criteria for lesion measurement method of evaluation of response and definition of response are the same for irRC and RECIST 1.1 and are available in the RECIST 1.1 guidelines (Appendix 1).

14.2.2 New lesions and non-target lesions

In irRC a new lesion does not automatically indicate progressive disease.

New measurable lesions are added to the sum of diameters of the previously existing target lesions, and the sum of diameters is followed at each subsequent tumor assessment.

New measureable lesions are defined using the same criteria as for baseline target lesions in RECIST v1.1. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measurable lesions. Up to five new measurable (and a maximum of two per organ) are allowed in total and will be included in the overall tumor assessment.

Non-target lesions (baseline and new non-measurable lesions) are used primarily for determination of Complete Response (CR). The RECIST v1.1 definitions for the assessment of non-target lesions apply. A CR requires that all non-target lesions disappear (both those present at baseline and any new non-measurable lesions that have appeared during the study). If after worsening a non-target lesion becomes measurable, it should still be followed as a non-target lesion. Worsening of non-target lesions and new non-measurable lesions only indicate disease progression if there is unequivocal evidence of disease progression (Table 14-6).

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

To assess tumor response, the sum of diameters for all target lesions is calculated (at baseline and throughout the study). The diameters of any new measurable lesions are included in the sum of diameters at each assessment to provide the total tumor burden. At each assessment, percent change in the sum of diameters is calculated and compared to baseline or to nadir in order to evaluate the target lesion response (including new measurable lesions) (Section 14.2.4). This evaluation combined with the status of non-target lesions (baseline and new non-measurable lesions) is then used to determinate the overall lesion response (Table 14-6). The thresholds for irPR and irPD assessment are the same as for RECIST v1.1.

14.2.4 Definitions of response categories and evaluation of overall lesion response

In irRC, the overall response is primarily based on target lesions (baseline and new measurable lesions). The non-target lesions only contribute to define irCR, and irPD in the case of unequivocal progression, as shown below in Table 14-6.

Like in RECIST 1.1, irCR and irPR must be confirmed at a new assessment after at least 4 weeks. Unlike RECIST 1.1, irPD also requires confirmation at a new assessment after at least 4 weeks.

The response categories are defined as follows:

- Immune related Complete Response (irCR): Disappearance of all non-nodal target lesions and non-target lesions in two consecutive observations not less than 4 weeks apart. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm. (Sum of diameters may be greater than zero at the time of CR, if nodal lesions are included as target lesions).
- Immune related Partial Response (irPR): At least a 30% decrease in the sum of diameters of all target lesions including new target lesions in two consecutive observations not less than 4 weeks apart, taking as reference the baseline sum of diameters.
- Immune related Progressive Disease (irPD): At least a 20% increase in the sum of diameters of all measured target lesions including new measurable lesions. The irPD must be confirmed in a second evaluation not less than 4 weeks later, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline (nadir). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Worsening of non-target lesions (existing or new) only indicate PD when there is unequivocal evidence of progression, confirmed in a second evaluation not less than 4 weeks later.
- Immune related Stable Disease (irSD): Neither a sufficient shrinkage to qualify for irPR or irCR, nor an increase in lesions which would qualify for irPD.
- Unknown (UNK): Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a method significantly different from baseline that prevents reasonable comparison to the prior assessments.

Table 14-6 Overall response at each assessment

Target and new measurable lesions (Tumor burden), * (%)	Non-target lesions (both baseline and new non-measurable)	Overall lesion response
- 100	Absent	irCR[a]
- 100	Stable/not evaluated	irPR[a]
≤-30 [b]	Absent/Stable/not evaluated	irPR[a]
>-30 [b] and<+20 [c]	Absent/Stable/not evaluated	irSD
≥+20 [c]	Any	irPD[a]
Any	Unequivocal progression	irPD[a]

Target and new measurable lesions (Tumor burden), * (%)	Non-target lesions (both baseline and new non-measurable)	Overall lesion response

* the longest diameter of new measurable lesions is included in the calculation of the sum of longest diameters.
[a] To be confirmed after at least 4 weeks.
[b] From baseline
[c] From nadir

If the evaluation of any of the target lesions could not be made during follow-up, the overall status must be 'unknown' unless progression was documented.

If the evaluation of any non-target lesions is not made, and all target lesions disappeared, irCR cannot be determined and overall response must be "irPR".

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 irCR.

14.2.5 Only non-measurable disease at baseline

For patients with only non-measurable disease at baseline, unequivocal progression of non-target lesions will constitute an irPD (i.e. worsening of the overall tumor burden which is substantial enough to lead to discontinuation or change of therapy). In addition, the appearance of new lesions (measurable or non-measurable) consistent with unequivocal progression taking into account the overall disease burden will constitute an irPD. The absence of all non-target lesions and no new lesions will qualify for irCR. Otherwise the overall response will be considered as irNon-CR/Non-PD (irNCRNPD) similar to RECIST 1.1. Confirmation of irPD and irCR as specified above in Section 14.2.4 is required. If any baseline non-target lesion or a new lesion observed at an earlier post-baseline evaluation was not/could not be assessed at a later post-baseline tumor evaluation then the overall response will be irUNK. No confirmation is required for irNCRNPD.

14.2.6 References (available upon request)

Bohnsack O, Ludajic K, Hoos A (2014) Adaptation of the immune-related response criteria: irRECIST. ESMO 2014; Abstract 4958 visible at: //webges.com/cslide/library/esmo/browse/search/eTT#9faE02tu.

Nishino M, Giobbie-Hurder A, Gargano M, et al (2013) Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res; 19:3936-3943.

Wolchok JD, Hoos A, O'Day S et al (2009) Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res; 15:7412-20.

14.3 Appendix 3: Statistical Details for the Phase Ib Part: Bayesian logistic regression model (BLRM): prior and design properties for hypothetical data scenarios

This appendix provides details of the statistical model, the derivation of prior distributions from historical and pre-clinical data, the results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model.

14.3.1 Statistical Models

The statistical model comprises single-agent toxicity parts, which allow the incorporation of single-agent toxicity data, and an interaction part.

14.3.1.1 Single agent part

Let $\pi_1(d_1)$ be the risk of DLT for MCS110 given as a single agent at dose d_1; $\pi_2(d_2)$ be the risk of DLT for PDR001 given as a single agent at dose d_2. These single agent dose-DLT models are logistic:

$$\text{MCS110: } \text{logit}\big(\pi_1(d_1)\big) = \log(\alpha_1) + \beta_1 \log(d_1/d_1^*)$$

$$\text{PDR001: } \text{logit}\big(\pi_2(d_2)\big) = \log(\alpha_2) + \beta_2 \log(d_2/d_2^*)$$

where d_1^*= 5 mg/kg and d_2^*= 300 mg (reference doses) are used to scale the doses of MCS110 and PDR001, respectively. Hence, α_1 and α_2 (>0) are the single-agent odds of a DLT at d_1^* and d_2^*, respectively; and β_1 and β_2 (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

14.3.1.2 Interaction

Under the situation of no interaction, the risk of a DLT at dose d_1 of MCS110 and dose d_2 of PDR001 is:

$$\pi_{12}^0(d_1, d_2) = 1 - \big(1 - \pi_1(d_1)\big)\big(1 - \pi_2(d_2)\big)$$

To allow for interaction between MCS110 and PDR001, an odds multiplier is introduced. The risk of DLT for combination dose (d_1, d_2) is then given by:

$$\text{odds}\big(\pi_{12}(d_1, d_2)\big) = \exp(\eta_{12} \times d_1/d_1^* \times d_2/d_2^*) \times \text{odds}\big(\pi_{12}^0(d_1, d_2)\big)$$

where $\text{odds}(\pi) = \pi/(1-\pi)$; and η_{12} is the log-odds ratio between the interaction and no interaction model at reference doses. Here $\eta_{12} = 0$ corresponds to no interaction, with $\eta_{12} > 0$ and $\eta_{12} < 0$ representing synergistic and antagonistic toxicity respectively.

14.3.2 Prior specifications

The Bayesian approach requires the specification of prior distributions for all model parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for MCS110, $\log(\alpha_2)$, $\log(\beta_2)$ for PDR001, and the interaction parameter η_{12}. A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters.

14.3.2.1 Prior distribution for the logistic parameters

For each of MCS110 and PDR001 single agent, a mixture prior was derived.

A MAP approach was used to incorporate the dose-DLT data from [CMCS110A2101] (first-in-human MCS110 study in prostate cancer patients) and [CMCS110X2201] (a Phase II study in PVNS patients, with the cutoff date Nov 28, 2015) for MCS110; and [CPDR001X2101] (first-in-human PDR001 oncology study, with the cutoff date Nov 28, 2015) for PDR001. To make the prior more robust, an additional mixture component corresponding to high toxicity was introduced.

14.3.2.1.1 Description of the meta-analytic-predictive (MAP) approach

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $\left(\log(\alpha^*),\ \log(\beta^*)\right)$ of the new trial using DLT data from historical studies.

Let r_{ds} and n_{ds} be the number of patients with a DLT, and the total number of patients at dose d in historical trial s ($s = 1, \ldots, S$). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

$$r_{ds} \mid \pi_{ds} \sim \text{Bin}(\pi_{ds}, n_{ds})$$

$$\text{logit}(\pi_{ds}) = \log(\alpha_s) + \beta_s \log(d/d^*)$$

$$\left(log(\alpha_s), log(\beta_s)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi), \qquad \text{s} = 1, \ldots, S$$

$$\left(log(\alpha^*), log(\beta^*)\right) \mid \mu, \psi \sim \text{BVN}(\mu, \psi)$$

The parameters $\mu = (\mu_1, \mu_2)$ and ψ are the mean and between-trial covariance matrix for the logistic parameters, the latter with standard deviations τ_1, τ_2, and correlation ρ. The parameters τ_1 and τ_2 quantify the degree of between trial heterogeneity. The following priors will be used for these parameters:

- normal priors for μ_1 and μ_2,
- log-normal priors for τ_1 and τ_2, and
- a uniform prior for ρ.

The MAP prior for single-agent model parameters in the new trial, $\left(\log(\alpha^*), \log(\beta^*)\right)$, is the predictive distribution

$$\left(log(\alpha^*), log(\beta^*)\right) \mid (r_{ds}, n_{ds} : s = 1, \ldots, S)$$

Since the predictive distribution is not available analytically, MCMC is used to simulate values from this distribution. This is implemented using JAGS version 3.12. The sample from this distribution is then approximated by a mixture of bivariate normal (BVN) distributions. BVN mixtures with increasing numbers of mixture components are fitted to the sample using the expectation-maximization (EM) algorithm (Dempster 1977). The optimal number of components of the mixture is then identified using the Akaike information criterion (AIC) (Akaike 1974).

14.3.2.1.2 Single agent MCS110

For MCS110, this study uses a mixture prior consisting of two components. Component 1 is the distribution derived based on dose-DLT data from [CMCS110A2101] (first-in-human MCS110 study in prostate cancer patients) and [CMCS110X2201] (a Phase II study in PVNS patients) by MAP approach (Section 14.3.2.1.1). The assigned weight for Component 1 is 80%. Component 2 allows for a higher toxicity case. The assigned weight for Component 2 is 20%.

Component 1:

For the MAP model for MCS110, reference dose $d_1^* = 5$ mg/kg is used, and data from $S = 2$ historical studies is available. (Table 14-8 and Table 14-9) [CMCS110A2101] is a Phase I study with 3 prostate cancer patients with bone metastasis receiving 0.01 mg/kg MCS110 in a once every 2 week dosing schedule on a 28-day cycle for 3 cycles. [CMCS110X2201] is a Phase II proof of concept study in patients with PVNS (pigmented villonodular synovitis). As of Nov-28-2015, there are 18 patients treated with single dose of MCS110 at 10 mg/kg.

Weakly informative normal priors are assumed for μ_1 and μ_2, with means corresponding to a risk of DLT of 10% at the reference dose, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to large between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014).

The prior distributions for the model used for deriving the MAP priors are specified in Table 14-7.

Table 14-7 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent MCS110 model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(0.10), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = log(1), sd = log(2)/1.96)
τ_2	log-normal(mean = log(0.500), sd = log(2)/1.96)
ρ	uniform(-1,1)

Historical data

Table 14-8 Historical data from [CMCS110A2101]

Dose level of MCS110 (mg/kg)	Number DLTs/Number of evaluable patients
0.01	0/3

Table 14-9 Historical data from [CMCS110X2201]

Dose level of MCS110 (mg/kg)	Number DLTs/Number of evaluable patients
10	0/18

Component 2:

This weakly informative bivariate normal prior allows for a case with higher toxicity.

- For the intercept parameter log(α_2), the prior mean of -1.658 is derived based on the a-priori median of an assumed 16% DLT rate at the reference dose d_2*= 5 mg/kg. By setting the standard deviation =2, the respective 95% a-priori interval for probability of DLT at dose 5 mg/kg is wide (0.4%, 90.6%), which represents weak prior information.
- For the log-slope parameter log(β_2), the prior mean of 0 and prior standard deviation of 1 allow for very flat to very steep slopes. Therefore, it is a weakly informative prior. The interpretation is as follows: when tripling the dose, the odds of having a DLT are multiplied by a factor of 3^{β}.
- The Component 2 is set to be (-1.658, 0, 2, 1, 0)

14.3.2.1.3 Single agent PDR001

For PDR001, this study uses a mixture prior consisting of three components. Component 1and 2 are derived based on dose-DLT data from First-in-human PDR001 oncology study [CPDR001X2101] by MAP approach (Section 14.3.2.1.1). The assigned total weight for Component 1 and 2 is 80%. Component 3 allows for a higher toxicity case. The assigned weight for Component 3 is 20%.

Component 1 and 2

For the MAP model for PDR001, reference dose $d_2^* = 300$ mg is used, and data from $S = 1$ historical study is available. (Table 14-11) [CPDR001X2101] is a Phase I study with two dose schedules: three cohorts of patients on a Q2W schedule; and two cohorts on a Q4W schedule. PDR001 dose levels in Q2W and Q4W dosing schedules are converted to Q3W by finding out the dose level in Q3W which provides equivalent area under the curve ($AUC_{0\text{-}6weeks}$) for dose levels in Q2W and Q4W regimens studied in [CPDR001X2101] trial. Using the popPK model developed from [CPDR001X2101] PK data following steps are conducted: (1) Target AUCs are simulated for studied dose levels in [CPDR001X2101] trial at their respective regimens for $AUC_{0\text{-}6weeks}$; (2) Corresponding Q3W $AUC_{0\text{-}6weeks}$ are generated for dose levels every 10 mg on Q3W regimen; i.e 50 through 2000 mg with every 10 mg interval; (3) The dose level on Q3W regimen that minimized the absolute difference between target AUC and Q3W $AUC_{0\text{-}6weeks}$ are selected as candidate dose.

After the dose conversion is performed as described above, PDR001 single agent data is then used to derive MAP prior. Firstly, weakly informative priors are assumed for μ_1 and μ_2, with means corresponding to a risk of DLT at the reference dose of 10%, and a doubling in dose leading to a doubling in the odds of the risk of a DLT, respectively. Priors for τ_1 and τ_2 are assigned such that (1) their medians correspond to substantial between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014). PDR001 data was then used to update the prior described above.

The prior distributions for the model used for deriving the MAP priors are specified in Table 14-10.

Table 14-10 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent PDR001 model parameters

Parameter	Prior distribution
μ_1	N(mean = logit(0.10), sd = 2)
μ_2	N(mean = 0, sd=1)
τ_1	log-normal(mean = 0.500, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.250, sd = log(2)/1.96)
ρ	uniform(-1,1)

Historical data

Table 14-11 Historical data from [CPDR001X2101]

Dose schedule	Dose level (mg/kg)	Flat dose (mg)	Equivalent dose level in Q3W (mg)*	Total Number of DLT /Number of evaluable patients
Q2W	1	80	110	0/16
Q2W	3	240	330	0/12
Q2W	10	800	1110	0/3
Q4W	3	240	220	0/6
Q4W	5	400	360	0/6

* Equivalent dose level in Q3W is calculated based on simulation described under Component 1 and 2

Component 3:

This weakly informative bivariate normal prior allows for a case with higher toxicity.

- For the intercept parameter $\log(\alpha_2)$, the prior mean of -1.099 is derived based on the a-priori median of an assumed 25% DLT rate at the reference dose d_2*= 300 mg. By setting the standard deviation =2, the respective 95% a-priori interval for probability of DLT at dose 300 mg/kg is wide (0.7%, 94.4%), which represents weak prior information.
- For the log-slope parameter $\log(\beta_2)$, the prior mean of 0 and prior standard deviation of 1 allow for very flat to very steep slopes. Therefore, it is a weakly informative prior. The interpretation is as follows: when tripling the dose, the odds of having a DLT are multiplied by a factor of 3^{β}.
- The Component 3 is set to be (-1.099, 0, 2, 1, 0)

All the information to derive the prior distributions for the model parameters is provided in Table 14-13.

14.3.2.2 Prior distribution for the interaction parameters

Although no interaction is expected, considerable uncertainty remains. A normal prior distribution for the interaction parameter η_{12} is to be derived to reflect the current uncertainty about the toxicity profile of the combination of MCS110 and PDR001. The risk of significant positive interaction between MCS110 and PDR001 cannot be totally excluded. The interaction parameter η_{12} was chosen accordingly but with a degree of uncertainty in order to allow for the

possibility that the interaction may be positive or negative. Therefore the following assumption is made for the interaction parameter:

- η_{12} is normally distributed, with mean 0, and standard deviation 2.803;
- At the starting dose of d_{1start}=3 mg/kg and d_{2start}=100 mg the corresponding distribution for the odds ratio has mean 1 and a 97.5th percentile of 3.00, i.e. 3-fold increase in odds of DLT due to interaction compared to no interaction.

Since the interaction is dose-dependent (see model definition in Section 10.4.2), the prior for the interaction parameter has a simple interpretation only at the anticipated combination reference dose of MCS110 = 5 mg/kg and PDR001 = 300 mg. Table 14-12 shows the prior median and 95% confidence interval of fold increase in odds of DLT due to interaction compared to no interaction at all provisional dose levels, as well as the reference dose level.

Table 14-12 A priori interaction at the provisional and reference dose levels

MCS110 (mg/kg, Q3W)	**PDR001 (mg, Q3W)**	
	100	**300**
3	1 (0.333, 3.000)	1 (0.037,27.000)
5	1 (0.160, 6.240)	**1 (0.004, 243.000)**
10	1 (0.026, 38.941)	1 (0.000,59049.000)
* Presented are median (95% confidence interval). The prior median of fold increase in odds of DLT with 95% confidence interval at the combination reference dose level is highlighted in bold.		

14.3.2.3 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 14-13.

Prior summaries for DLT rates for are summarized in Table 14-14.

Table 14-13 Prior distribution for the model parameters

Parameter	**Mean**	**Standard deviations**	**correlation**	**weight**
Single agent MCS110 prior				
BVN Mixture $(\log(\alpha_1), \log(\beta_1))$				
Component 1 (MAP prior)	(-4.302 , -0.356)	(1.852, 1.030)	-0.050	0.80
Component 2 (high toxicity)	(-1.658 , 0)	(2, 1)	0	0.20
Single agent PDR001 prior				
BVN Mixture $(\log(\alpha_2), \log(\beta_2))$				
Component 1 (MAP prior)	(-5.166 , -0.582)	(1.454, 0.956)	-0.275	0.43
Component 2 (MAP prior)	(-4.115 , -0.008)	(1.083, 0.647)	-0.212	0.37
Component 3 (high toxicity)	(-1.099 , 0)	(2, 1)	0	0.20

Parameter	Mean	Standard deviations	correlation	weight
Interaction parameter				
Normal				
η_{12}	0	2.803	N/A	N/A

Table 14-14 Summary of prior distribution of DLT rates

MCS110 dose (mg/kg)	Prior probabilities that P(DLT) is in the interval :					Quantiles		
	[0, 0.16)	[0.16, 0.33)	[0.33,1]	Mean	SD	2.5%	50%	97.5%
	In combination with PDR001 100 mg							
3	0.803	0.093	0.104	0.111	0.187	0.001	0.03	0.747
5	0.74	0.11	0.15	0.145	0.22	0.001	0.044	0.845
10	0.604	0.117	**0.279**	0.244	0.309	0.001	0.082	0.981
	In combination with PDR001 300 mg							
3	0.687	0.112	0.201	0.183	0.262	0.001	0.052	0.932
5	0.601	0.104	**0.295**	0.256	0.328	0	0.074	0.988
10	0.516	0.063	**0.421**	0.381	0.418	0	0.131	1

Note: bold values indicate dose combinations not meeting the overdose criterion.

14.3.3 Hypothetical on-study scenarios

To illustrate the performance of the Bayesian model used to guide dose escalation, hypothetical dose escalations scenarios following the provisional dose levels specified in Table 6-2 are displayed. In each case, the maximum dose that can be used in the next cohort of patients is shown. This maximum dose is determined using the model based assessment of the risk of DLT in future patients and the dose escalation rules as described in Section 6.2.3. In practice a dose below the maximum might be chosen based on additional safety, PK or PD information (Section 6.2.3).

Table 14-15 shows on-study dosing recommendations for some hypothetical data scenarios.

Note that the next dose combination is selected in concordance with the provisional dose levels specified in Section 6.2.2 of the protocol wherever it is allowed, to mimic possible on-study escalation steps.

Table 14-15 Dose decisions recommended by BLRM under EWOC

Scenario	Dose combination MCS110 (mg/kg)/PDR001 (mg)	Number of patients	Number of DLTs	Next dose level: Dose (mg/kg / mg)	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
1	Cohort1:3/100	3	0	3/300	0.101	0.097	0.031
2	Cohort1:3/100	3	1	3/100	0.260	0.219	0.150
3	Cohort1:3/100	3	2	STOP			
4	Cohort1:3/100 Cohort2:3/100	3 5	1 0	3/300	0.189	0.212	0.110
5	Cohort1:3/100 Cohort2:3/300	3 5	0 0	5/300	0.075	0.061	0.014

Scenario	Dose combination MCS110 (mg/kg)/PDR001 (mg)	Number of patients	DLTs	Next dose level Dose (mg/kg / mg)	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
6	Cohort1:3/100 Cohort2:3/300	3 5	0 1	3/300	0.256	0.092	0.109
7	Cohort1:3/100 Cohort2:3/300	3 5	0 2	3/100	0.175	0.043	0.075
8	Cohort1:3/100 Cohort2:3/300 Cohort3:3/300	3 5 4	0 1 0	5/300	0.199	0.200	0.110
9	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300	3 5 4	0 0 0	10/300	0.055	0.104	0.003
10	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300	3 5 4	0 0 1	5/300	0.263	0.125	0.119
11	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300	3 5 4	0 0 2	3/300	0.255	0.030	0.110
12	Cohort1:3/100 Cohort2:3/300 Cohort3:3/300 Cohort4:5/300	3 5 4 3	0 1 0 1	3/300	0.222	0.015	0.102
13	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300 Cohort4:3/300	3 5 4 3	0 0 2 1	3/300	0.380	0.048	0.144
14	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300 Cohort4:10/300	3 5 4 6	0 0 0 1	10/300	0.244	0.086	0.101
15	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300 Cohort4:10/300	3 5 4 6	0 0 0 2	5/300	0.081	0.002	0.067
16	Cohort1:3/100 Cohort2:3/300 Cohort3:5/300 Cohort4:10/300 Cohort5:5/300	3 5 4 6 3	0 0 0 2 1	5/300	0.163	0.005	0.094
Note that the overdose criterion is defined as P(over) < 0.25. *Additional dose levels may be added if allowed by the BLRM.							

Within Table 14-15, it can be seen that the model generally leads to decisions that are in agreement with clinical sense. The dose levels investigated correspond to the provisional dose levels specified in Section 6.2.2.

14.3.4 Operating characteristics for MCS110 + PDR001 combination arm

A simulation study is used to illustrate the long run performance of the Bayesian dose escalation model. Several example scenarios were investigated (Section 14.3.4.1), and in each case 1000 trials were simulated, with results summarized in Section 14.3.4.3.

14.3.4.1 Scenarios

In order to show how the design performs, 3 hypothetical scenarios were investigated:

1. For scenario 1, the odds of DLT are aligned with the prior information, i.e. the DLT rates for dose combinations are set to the median values derived from the prior.
2. For scenario 2, the odds of DLT are assumed to be 100% increase from scenario 1
3. For scenario 3, the odds of DLT are assumed to be 4-folds increase from scenario 1

To note, under scenario 1, there's not any dose level have DLT rate falls into target or over-toxic DLT interval. Therefore, we didn't explore any scenarios which assume smaller odds of DLT than scenario 1. Under scenario 2, there's only one combination dose level fall into target toxicity interval and no over-toxic DLT rate. Under scenario 3, there are three combination dose levels fall into target toxicity interval and one over-toxic DLT rate.

The true probabilities used in the simulation are presented in Table 14-16 for each scenario above.

Table 14-16 True underlying cumulative probabilities of DLT for different scenarios

	PDR001 (mg)	
MCS110 (mg/kg)	**100**	**300**
Scenario 1		
0.3	0.013	0.026
1	0.018	0.033
3	0.030	0.052
5	0.044	0.074
10	0.082	0.131
Scenario 2		
0.3	0.026	0.051
1	0.035	0.064
3	0.058	0.099
5	0.084	0.138
10	0.152	**0.232**
Scenario 3		
0.3	0.050	0.096
1	0.068	0.120
3	0.110	**0.180**
5	0.155	**0.242**
10	**0.263**	0.376

- Grey shaded cells indicate True probability fall within target interval (0.16, 0.33]

14.3.4.2 Simulation details

1000 trials were used to simulate each scenario. The starting dose combination was chosen as 3 mg/kg for MCS110 and 100 mg for PDR001, and the maximal dose to jump to was orthogonal, and follows the protocol specifications (Section 10.4.2 of the protocol). The number of patients to enroll in each cohort and stopping rules used to declare MTD were defined as:

- Maximum number of patients treated: 60

- Minimum cohort size: 3
- Minimum number of patients treated at a given dose combination in order to declare MTD: 6
- Posterior probability of targeted toxicity at this combination dose > 50% and is the highest among potential doses, or
- Minimum number of patients treated in the trial: 15

Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance under each true scenario. The metrics reviewed were:

1. Average proportion of patients receiving a target dose combination on study (I)
2. Average proportion of patients receiving a dose combination with true P(DLT) ≥ 33% on study (II)
3. Average proportion of patients receiving a dose combination with true P(DLT) < 16% on study (III)
4. Proportion of trials that were recommended a target dose combination as the MTD (IV)
5. Proportion of trials that were recommended a dose combinations with true P(DLT) ≥ 33% as the MTD (patient risk) (V)
6. Proportion of trials that were recommended a dose combination with true P(DLT) < 16% as the MTD (VI)

14.3.4.3 Simulation results

Table 14-17 below summarizes the simulated operating characteristics of the model for the 3 different scenarios studied, additionally showing the percentage of trials stopped before declaring MTD when all dose combinations were considered too toxic.

Table 14-17 Results

Scenario	Metric						
	I	II	III	IV	V	VI	Stopped
1	0.000	0.000	1.000	0.000	0.000	0.998	0.002
2	0.128	0.000	0.872	0.098	0.000	0.897	0.005
3	0.455	0.065	0.480	0.603	0.040	0.333	0.024

The simulated operating characteristics presented show that the combination model performs reasonably and well under the hypothetical scenarios investigated.

Scenario 1:

Since there's no dose combination which has median DLT rate in the target or over toxicity intervals, no patient receive a target dose or over-toxic dose combination (metric I and II) on study, and no trial was recommended with a target dose or over-toxic dose as MTD (metric IV and V). Under this scenario, since both study drugs demonstrate good safety profile with low DLT rate (<16%), it may be expected to identify a RP2D before identifying the MTD.

Scenario 2:

The proportion of patients receiving target dose is low (12.8%) as is the proportion of trial with target dose as recommended dose (9.8%). This is because only the highest combination dose (MCS110=10 mg/kg and PDR001=300 mg) falls into the target toxicity interval [16%, 33%). Further investigation reveals that there are additionally 54.4% of trials with MTD dose identified at just one dose level below the target dose (MCS110=5 mg/kg, PDR001=300 mg or MCS110=10 mg/kg, PDR001=100 mg). Of note, the probability of DLT for these dose combinations lies just below the lower limit of the target interval.

Scenario 3:

The proportion of patients receiving target dose is 45.5% and proportion of trial with target dose as recommended dose 60.3%. Further investigation reveals that there are additionally 22.8% of trials with MTD dose identified at just one dose level below the target dose (MCS110=5 mg/kg, PDR001=100 mg or MCS110=1 mg/kg, PDR001=300 mg). The proportion of patients receiving a dose combination with true P(DLT) ≥ 33% or trials that were recommended a dose combinations with true P(DLT) ≥ 33% as the MTD (patient risk) is very low (metric II: 6.5% and metric V: 4%)

In all scenarios, the percentages of trials that were stopped when all dose combinations were considered too toxic are low (< 3%) in all scenarios.

In conclusion, the simulations performed illustrate that the model has good operating characteristics.

14.3.5 References (available upon request)

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