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ACZ885

Clinical Trial Protocol CACZ885U2301

A randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of pembrolizumab plus platinum-based doublet chemotherapy with or without canakinumab as first line therapy for locally advanced or metastatic non-squamous and squamous non-small cell lung cancer subjects (CANOPY-1)

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List of abbreviations

ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANC	Absolute Neutrophil Count
ASMA	Anti-Smooth Muscle Antibody
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
b.i.d.	bis in die/twice a day
BDR	Bioanalytical Data Report
BIRC	Blinded Independent Review Committee
BLQ	Below the Limit of Quantification
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
BOR	Best Overall Response
BRAF	B-raf proto-oncogene
BUN	Blood Urea Nitrogen
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CAPS	Cryopyrin Associated Periodic Syndromes
Cavg	Average concentration
CD-transferrin	Carbohydrate Deficient-transferrin
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CHF	Congestive Heart Failure
CI	Confidence Interval
Cmax	Maximum concentration
Cmin	Minimum concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
COAs	Clinical Outcome Assessments
CPD	Confirmed Progressive Disease
CR	Complete Response
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive Protein
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
CT	Computer Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events

CTCs	Circulating Tumor Cells
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
CTx	Chemotherapy
CV	Coefficient of variation
CVD	Cardiovascular Disease
CxDx	Cycle x Day x
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DCR	Disease Control Rate
DDI	Drug-Drug Interactions
DDS	Dose-Determination Set
DILI	Drug Induced Liver Injury
DLRT	Dose Level Review Team
DLTs	Dose Limiting Toxicities
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DoR	Duration of Response
e.g.	exempli gratia
EBV	Epstein-Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
ELISA	Enzyme-linked immunosorbent assay
EMA	European medicines agency
EOI	End of Infusion
EORTC	European Organisation for Research and Treatment of Cancer
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcomes
ERCP	Endoscopic Retrograde Cholangiopancreatography
EU	European Union
EU CTR	European Union Clinical Trial Regulation
EWOC	Escalation With Overdose Control
FAS	Full Analysis Set
FDA	Food and Drug Administration
FMF	Familial Mediterranean Fever
FPFV	First Patient First Visit
G-CSF	Granulocyte Colony-Stimulating Factor
gamma(γ)-GT	gamma-glutamyl transferase
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyltransferase
h	Hour
HAV	Hepatitis A Virus

HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HEV	Hepatitis E Virus
Hgb	Hemoglobin
HIDS	Hyperimmunoglobulin D Syndrome
HIV	Human immunodeficiency virus
HR	Hazard Ratio
hs-CRP	High-sensitivity C-reactive protein
hs-IL-6	High sensitivity interleukin 6
HSV	Herpes Simplex Virus
i.e.	id est
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
iCPD	Immune Confirmed Progressive Disease
iCR	Immune related complete response
iDCR	Immune related disease control rate
IEC	Independent Ethics Committee
IG	Immunogenicity
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-1β	Interleukin-1β
IMP	Investigational Medicinal Product
IN	Investigator Notification
INN	International Nonproprietary Names
INR	International Normalized Ratio
iORR	Immune related overall response rate
iPFS	Immune related progression-free survival
iPR	Immune related partial response
irAE	Immune-related adverse events
IRB	Institutional Review Board
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IRT	Interactive Response Technology
iSD	Immune related stable disease
iSOD	Immune sum of diameters
IUD	Intrauterine Device
iUPD	Immune Unconfirmed Progressive Disease
IUS	Intrauterine System
LDH	Lactate dehydrogenase
LFT	Liver Function Test

LLN	Lower Limit of Normal
LPLV	Last Patient Last Visit
MACE	Major Adverse Cardiovascular Events
MCV	Mean Corpuscular Volume
MDSCs	Myeloid Derived Suppressor Cells
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Myocardial Infarction
MKD	Mevalonate Kinase Deficiency
mL	milliliter(s)
mPFS	median Progression Free Survival
MRI	Magnetic Resonance Imaging
NASH	Nonalcoholic steatohepatitis
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse events
NE	Non Estimable
NF-κB	Nuclear Factor Kappa Beta
NLNT	New Lesion Non-Target
NLT	New Lesion Target
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
NSCLC	Non-Small Cell Lung Cancer
OLE	Open Label Extension
ORR	Overall Response Rate
OS	Overall Survival
p.o.	Per os (oral administration)
PAS	Pharmacokinetic Analysis Set
PBO	Placebo
PD	Pharmacodynamic(s) Progressive disease
PD-L1	Programmed death-ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
PROs	Patient Reported Outcomes
PT	Prothrombin time
QMS	Quality Management System
QxW	Every x weeks
R-value	ALT/ALP in multiples of ULN
RBC	Red blood cell(s)
RECIST	Response Evaluation Criteria in Solid Tumors
ROS-1	c-ros oncogene 1
RP2D	Recommended Phase 2 Dose
RP3R	Recommended Phase 3 dose Regimen
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRI	Safety run-in
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	The elimination half life associated with the terminal slope (lz) of a semi logarithmic concentration time curve (time)
T1D	Type 1 Diabetes
T3	Triiodothyronine
T4	Thyroxine
TAMs	Tumor Associated Macrophages
TB	Tuberculosis
TBIL	Total Bilirubin
Tmax	The time at which the maximum observed concentration (Cmax) occurs
TNF	Tumor Necrosis Factor
TNFα	Tumor necrosis factor alpha
TP	Time-point
TRAPS	Tumor Necrosis Factor Receptor Associated Periodic Syndrom
TSH	Thyroid-Stimulating Hormone
TTR	Time To Response
ULN	Upper limit of normal
US	United States
USPI	US-Package Insert
VATS	Video-Assisted Thoracic Surgery
VEGF	Vascular Endothelial Growth Factor
vs.	Versus
WBC	White blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug 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.
Data (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 samples.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject 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).
Implementation of protocol amendment	The implementation of a protocol (or protocol amendment) for a subject at a specific site is permitted when relevant Health Authority and/or Ethics Committee(s) approvals have been obtained as applicable and when the subject has signed the required informed consent(s).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug(s)	Any drug (or combination of drugs) administered to the subject as part of the required study treatment; includes investigational drug.
Study treatment	All study drugs administered to the subject (includes investigational drug)

Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.
Withdrawal of informed consent and exercise of participants' data privacy rights	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data.

Amendment 6 (25-Aug-2023)

Amendment rationale

As of 25-Aug-2023, there are 18 subjects on treatment, 5 of them receiving canakinumab in combination with pemetrexed, 6 receiving canakinumab alone, and 7 receiving pemetrexed alone.

The main objective of amendment 06 is to ensure continuous provision of canakinumab for subjects who in the opinion of investigator are still deriving clinical benefit, by adding one additional pharmaceutical form for canakinumab.

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.

The following changes are implemented:

- List of abbreviations: Removed the abbreviation "CMO&PS" as it is replaced with "Novartis Safety" throughout the document, in accordance with the global protocol template. Added the abbreviation "IMP".
- Section 1.2: As of 30-Jun-2023, confirmed that there were no changes to the overall safety and tolerability profile of canakinumab, platinum-based chemotherapy and pembrolizumab.
- Section 3, Figure 3-2: Updated footnote 3 to clarify that OLE phase was never implemented since the study did not meet its primary endpoints of Overall Survival (OS) and Progression Free Survival (PFS) at final analysis. Additionally, clarified that all subjects will enter Safety follow-up period of 130 days once dosing is discontinued.
- Section 4.1, Table 4-1: Clarified that all subjects will enter Safety follow-up period of 130 days once dosing is discontinued.
- Section 4.2.4: Updated with information that the study CPDR001X2102 is completed.
- Section 4.7: The new section to define the end of the study is added per alignment with global protocol template.
- Section 6.1.1.4: Updated information regarding the status of ongoing subjects. Table 6-6 is the new table for investigational and study drugs post implementation of protocol amendment 06 and contains two canakinumab pharmaceutical forms (200 mg/1.33 mL solution for s.c. injection as pre-filled syringes and 150 mg/1 mL solution for injection in vial) and pemetrexed. Consequently, table numbering in Section 6 is updated.
- Section 6.1.1.5: Updated with the information that canakinumab pharmaceutical form of 150 mg/1 mL solution for injection in vial will be supplied once protocol amendment 06 is implemented and canakinumab 200 mg/1.33 mL solution for s.c. injection as pre-filled syringes is no longer available. Also, confirmed that the dose of canakinumab to be given in this current study is unchanged (200 mg s.c). The available data to support transition to the new ACZ885 drug formulation (150 mg/1 mL solution for s.c. injection in vial) is added. Additionally, ACZ885 dosing in Table 6-5 is updated with Q6W frequency.
- Section 6.7: Updated with information that canakinumab pharmaceutical form of 150 mg/1 mL solution for injection in vial requires preparation before dosing.

- Section 8.3.1, Table 8-6: Clarified that the imaging assessment frequency will be until protocol-defined subject discontinuation or sponsor study termination.
- Section 8.4.1: Clarified that local safety evaluations are aligned with the standard of care of current treatment and dosing regimen.
- Section 9: Updated title and requirements, procedures, and data collection for study discontinuation, per the global protocol template.
- Section 9.2: Addition of the new section to define participant discontinuation from the study, per the global protocol template.
- Section 10.1.1: Provided additional clarification of the adverse events, as per the global protocol template.
- Section 10.1.1.2: Updated version of the ICH guidelines, per the global protocol template.
- Section 12.5.3: Replaced the abbreviation PAS with the full name (Pharmacokinetic Analysis Set).
- Editorial revisions and text corrections were also included throughout the document.

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 and Health Authority approval according to local regulations 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 5 (01-Dec-2022)

Amendment rationale

Enrollment for the safety run-in part was closed on 20-Mar-2019, with 30 subjects enrolled. As of 08-Dec-2021, all subjects from the safety run-in have discontinued the study. Enrollment for the randomized part was closed on 11-Dec-2019, with 643 subjects randomized. As of 01-Dec-2022, there are 29 subjects on treatment, 10 of them receiving canakinumab in combination with pemetrexed, 9 receiving canakinumab alone, and 10 receiving pemetrexed alone.

As of 25-Oct-2021, the study did not meet its primary endpoints of Overall Survival (OS) and Progression Free Survival (PFS) at final analysis. The trial was unblinded and subjects were allowed to continue treatment with pembrolizumab and pemetrexed plus canakinumab (as applicable) if the investigator considered this beneficial for the subject.

The main objectives of amendment 05 are to:

- Ensure continuous provision of canakinumab for subjects who in the opinion of investigator are still deriving clinical benefit, by adding one additional pharmaceutical form for canakinumab
- Align safety and efficacy assessment schedule to standard of care
- Define the new end of study, as when all subjects discontinue the study treatment and complete their safety follow up, die, withdraw consent, or are lost to follow up, whichever comes first

In addition, the following changes are implemented:

- Replacement of central safety laboratory with local safety laboratory
- Removal of Patient Reported Outcomes (PRO) collections
- Removal of all PK, PD, IG samples collections
- Removal of all biomarkers samples collections
- Removal of efficacy follow-up
- Removal of 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.

- List of abbreviations: updated with EU Clinical Trial Regulation and removal of Rest of the World
- Glosary of terms: updated with the addition of assessment Implementation of the protocol amendment and update of the assessment name Withdrawal of informed consent and exercise of participants' data privacy rights
- Protocol summary table: updated to reflect the changes post implementation of protocol amendment 05
- Section 1.2: updated with the summary of primary analysis results

- Section 3: updated to reflect changes post implementation of protocol amendment 05: all subjects will enter or complete the safety follow-up but the subjects in efficacy or survival follow-up will discontinue the study
- Section 3, Figure 3-3: footnote updated for Efficacy follow-up and End of Treatment to reflect changes post implementation of protocol amendment 05
- Section 4.1, Table 4-1: updated with the protocol amendment 05 rationale
- Section 4.6: added new section "Rationale for public health emergency mitigation procedures"
- Section 6.1.1.4: added dosing regimen post implementation of protocol amendment 05. Renumbered Section 6.1.1.4 to Section 6.1.1.5 due to addition of Section 6.1.1.4.
- Section 6.1.1.4, Table 6-5: addition of the table with the dosing regimen post implementation of protocol amendment, and consequently updated Table numbering from Table 6-5 to Table 6-9
- Section 6.1.1.5: clarified that post trial unblinding on 25-Oct-2021, canakinumab-matching placebo was no longer supplied nor dispensed
- Section 6.1.1.5, Supply for study treatment: added pharmaceutical form of ACZ885
- Section 6.1.1.5, Administration of study treatment: removal of information on volume of drug syringes
- Section 6.1.1.5, Figure 6-2: update of the title. Clarified that post trial unblinding on 25-Oct-2021, canakinumab-matching placebo was no longer supplied nor dispensed
- Section 6.3: clarified that protocol sections related to subject numbering, treatment assignment and randomization are not applicable post implementation of protocol amendment 05
- Section 6.4: clarified that trial was unblinded 25-Oct-2021 prior to the implementation of protocol amendment 05
- Section 6.7: clarified that post trial unblinding on 25-Oct-2021, canakinumab-matching placebo was no longer supplied nor dispensed
- Section 7 and Section 8: added alternative methods of obtaining informed consent and providing continuing care during a Public Health emergency as declared by Local or Regional authorities
- Section 8, Table 8-5: added new assessment schedule post implementation of protocol amendment 05, and consequently updated Table numbering from Table 8-5 to Table 8-10
- Section 8.3.1: clarified that post implementation of protocol amendment 05, only the RECIST 1.1 response assessment will be recorded in the appropriate CRF page. Other efficacy assessments will be recorded in the source documentation only
- Section 8.3.1, Table 8-6: updated to reflect that no more efficacy follow-up will be performed post implementation of protocol amendment 05. Clarified that the frequency of tumor assessment post implementation of protocol amendment 05 is every 12 weeks
- Section 8.3.1.4: clarified that efficacy follow-up will not be performed post implementation of protocol amendment 05

- Section 8.3.3: clarified that survival follow-up will not be performed post implementation of protocol amendment 05
- Section 8.4: clarified safety and survival assessments post implementation of protocol amendment 05. Also, added information about alternative methods of safety monitoring during a Public Health emergency as declared by Local or Regional authorities
- Section 8.4.1: clarified that local laboratory will be used instead of central laboratory
- Section 8.4.1: addition of Table 8-8 with the safety assessment post implementation of protocol amendment 05. Updated title of Table 8-7. Also, added information about alternative methods of safety monitoring during a Public Health emergency as declared by Local or Regional authorities
- Section 8.4.1.1: clarified how the estimate of GFR will be done
- Section 8.4.3: clarified that the performance status will no longer be collected post implementation of protocol amendment 05.
- Section 8.4.4: clarified that ECGs should be performed per Table 8-5
- Section 8.4.5: clarified that only urine pregnancy test will be performed post implementation of protocol amendment 05. Also, clarified that serum pregnancy test will be used at EOT. Addition of the use of urine pregnancy test kits during a Public Health emergency as declared by Local or Regional authorities
- Section 8.5.1: clarified that ePRO questionnaires will no longer be collected post implementation of protocol amendment 05
- Section 8.5.2: clarified that the sample collection for analysis of PK (and PD/IG as applicable) will no longer be performed post implementation of protocol amendment 05
- Section 8.5.3: clarified that the sample collection for analysis of biomarkers will no longer be performed post implementation of protocol amendment 05
- Section 9.1.1: clarified that assessment schedule post implementation of protocol amendment 05 is per Table 8-5:
- Section 9.1.2: clarified reasons for withdrawal of consent. Addition of instructions of documenting the withdrawal of consent at the site level
- Section 9.1.3: clarified definition of subjects who are lost to follow-up
- Section 9.1.4: clarified reasons for early study termination. Removal of wording related to instructions for contacting the patient when subject should stop the drug since the instructions are present in the Section 9.1.1
- Section 9.2: definition of study end updated by removing the criteria of five years from the time of the last subject first treatment in the randomized part
- Section 10.1.3: updated with instructions on SAE reporting. Clarified that post implementation of protocol amendment 05, SAE reported post 130-day safety follow-up. Also, update of regulation for SUSARs reporting under EU CTR
- Section 11.2: addition of section related to data protection. Renumbered Section 11.2 to Section 11.3 and Section 11.3 to Section 11.4 due to addition of Section 11.2
- Appendix 16.6: update of safety follow-up chart for post implementation of protocol amendment 05
- Editorial revisions and text corrections were also included throughout the document

IRBs/IECs

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Amendment 4 (21-Aug-2020)

Amendment rationale

Enrollment for the safety run-in part was closed on 20-Mar-2019, with 30 subjects enrolled, of which 23 subjects discontinued the study as of 21-Aug-2020. Enrollment for the randomized part was closed on 11-Dec-2019, with 643 subjects randomized, of which 328 have discontinued the study as of 21-Aug-2020.

The main objective of amendment 04 is to:

- Create an open label extension phase (OLE) that all subjects still on treatment or in safety/efficacy follow-up will transition into, following unblinding of investigational sites to treatment allocation, if OS reaches statistical significance at one of the interim or final analyses. If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, OLE will be initiated after final OS analysis and following the unblinding of investigational sites. Subjects will transition to a reduced study assessment schedule.
- Allow subjects that were randomly allocated to the placebo arm the opportunity to cross over to the investigational drug (ACZ885), per investigator and subject discretion, during the OLE phase.
- Define the new end of study, as the end of the OLE phase, at 5 years from the time of last subject first treatment in the randomized part or when all subjects discontinue the study treatment and complete their safety follow up, die, withdraw consent or are lost to follow up, whichever comes first.

In addition, the following changes are implemented:

- To clarify that all laboratory events meeting the DILI criteria are to be reported as SAE in the absence of alternative explanation.
- To add that confirmed COVID-19 infection should be considered as medically significant AE and therefore should be reported as SAE.
- To add that in case that a female subject becomes pregnant, the study treatment should be stopped, and the subject must be asked to read and sign the pregnancy consent form. Also to change the newborn follow up period from “at least 12 months” to “up to 12 months”.

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.

- Protocol summary: updated to add the OLE phase
- Section 3: added new paragraph to describe the design of the OLE
- Section 3, Figure 3-2: updated title and Figure to include the optional crossover from canakinumab matching-placebo to canakinumab during the OLE
- Section 3, Figure 3-3: updated to include the OLE and clarified that safety follow up is every 26 days for 130 days after the last dose of the study treatment rather than after EOT
- Section 4, Table 4-1: added rationale for the OLE and updated wording that pembrolizumab treatment will be given for a maximum of 35 administrations and not cycles

- Section 6.1.1.3: added new section to describe dosing regimen during the OLE.
- Section 6, Figure 6-2: Title and footnote updated to include the optional crossover from canakinumab matching-placebo to canakinumab during the OLE.
- Section 6.1.3: added new paragraph to describe the criteria for the optional crossover of subjects from canakinumab matching-placebo to canakinumab during the OLE.
- Section 6.1.4: clarified that subjects randomized to the canakinumab matching-placebo arm will be allowed to cross over to canakinumab if the investigator determines this is in the subject's best interest and per subject discretion, provided they fullfill crossover criteria
- Section 6.1.4.1: Pembrolizumab treatment duration is a maximum of 35 administrations instead of cycles.
- Section 6.3.2: clarified that transition to OLE and crossover (if applicable) will be performed on the IRT system.
- Section 6.4: clarified that following unblinding of investigational sites and provided the primary objective is met, all subjects will transition to OLE
- Section 6.5.4.2: clarified that all laboratory events meeting the DILI criteria are to be reported as SAE in the absence of alternative explanation.
- Section 6.6.2: clarified that emergency unblinding will no longer be applicable following investigational site unblinding.
- Section 8, Table 8-2, Table 8-3, and Table 8-4: clarified that safety follow up is every 26 days for 130 days after the last dose of the study treatment rather than after EOT.
- Section 8, Table 8-4: added new assessment schedule for OLE, and consequently updated Table numbering from Tables 8-4 to 8-7.
- Section 8.3.1: clarified that imaging data for OLE should not be submitted to the imaging CRO.
- Section 8, Table 8-5: updated to clarify that the imaging assesment schedule during the OLE will remain the same as in SRI or randomized part until Week 159 (aprox. 3 years) after the study C1D1and then change to every 24 weeks.
- Section 8.3.1.2: clarified that the imaging assesment schedule during the OLE will remain the same as in SRI or randomized part until Week 159 (aprox. 3 years) after the study C1D1 and then change to every 24 weeks.
- Section 8.4.1: clarified that only local laboratory testing will be performed during the OLE
- Section 8, Table 8-6: updated to clarify which labolatory parameters are not applicable for the OLE.
- Section 8.4.5: clarified that only urine pregnancy testing is applicable during the OLE, and serum pregnancy test will be performed at EOT.
- Section 8.5.1: clarified that ePRO assesment will follow the same schedule as tumour assessments during the OLE.
- Section 8.5.2: clarified that there will be no PK, IG and PD sample collection during the OLE.
- Section 9.2: updated for the addition of the OLE phase and to define the new end of study.
- Section 10.1.2: added that confirmed COVID-19 infection should be considered medically significant and reported as SAE

- Section 10.1.4: clarified that in case of a female subject pregnancy, the study treatment should be stopped and the pregnancy form read and signed.
- Section 10.1.4: changed the newborn follow up period from at least 12 months to up to 12 months.
- Section 12: added that any additional data for ongoing subjects in the randomized part following the final OS analysis and data for subjects in OLE (if initiated) will be further summarized in a final study report.

Editorial revisions and text corrections were also included throughout the document

IRBs/IECs

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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 3 (08-Jan-2020)

Amendment rationale

Enrollment for the safety run-in part was closed on 20-Mar-2019, with 30 subjects enrolled. As of 08-Jan-2020, 15 subjects from the safety run-in part have discontinued the study. Enrollment for the randomized part of the study started on 10-Jun-2019 and finished on 11-Dec-2019. As of 08-Jan-2020, 637 subjects have been randomized, of which 73 have discontinued the study, while 12 subjects are still undergoing screening.

The main objective of amendment 03 is:

- To implement the Health Authority request that patients who have discontinued pembrolizumab due to toxicity or completed 35 cycles of pembrolizumab per protocol and develop RECIST 1.1 progressive disease while receiving chemotherapy combined with canakinumab/matching placebo cannot continue treatment with canakinumab/matching placebo with chemotherapy (during induction or maintenance), as there is no evidence to suggest that drug administration will provide clinical benefit in this setting. Chemotherapy refers to platinum-based doublet chemotherapy during induction or pemetrexed chemotherapy during maintenance.

In addition, the following changes are implemented:

- To clarify exclusion criterion #3 by removing the specific EGFR mutations listed in parenthesis, as exon 20 is not a EGFR sensitizing mutation.
- To clarify that female partners of male participants are also informed of the study treatment risk in case of pregnancy during the study
- To clarify that if a patient is not able to self-administer the ePRO questionnaires (e.g. due to illiteracy or blindness) the questionnaires will not be completed.
- To clarify that for subjects who continue receiving study treatment beyond initial RECIST 1.1 PD, radiation therapy is allowed.
- To replace the Adverse Event of Special Interest (AESI) name 'DILI (Hepatic transaminases and bilirubin elevations)' with the new AESI name 'Abnormal Liver Parameters' so as to reflect MedDRA search more accurately
- To clarify the scope of optional pharmacogenetic analysis.
- To add that if a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

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, Table 4-1: updated to add reference to section 6.1.4.1.
- Section 5.2: Exclusion #3 updated to remove reference to specific EGFR mutations, previously in parenthesis.
- Section 6.1.3: updated to clarify that all patients are expected to continue to maintenance canakinumab/matching placebo in combination with pembrolizumab and to remove reference to treatment beyond RECIST 1.1. PD

- Section 6.1.4.1: updated to clarify that if pembrolizumab is discontinued before RECIST 1.1 PD then canakinumab/matching placebo with chemotherapy (during induction or maintenance) is not allowed beyond RECIST 1.1 PD. Also removed previous provisions for treatment beyond RECIST 1.1 PD when pembrolizumab is discontinued during induction or during maintenance.
- Section 6.2.1.1.1: updated to clarify that after RECIST 1.1 PD, radiation therapy is allowed.
- Section 7: added the words " and female partners of male participants" to clarify that female partners of male participants are also informed of the study treatment risk in case of pregnancy during the study.
- Section 8.3.1.2: added reference to section 6.1.4.1.
- Section 8.5.1: updated to clarify that if a patient is not able to self-administer the ePRO questionnaires (e.g. due to illiteracy or blindness) then questionnaires will not be completed.
- Section 8.5.3.3: deleted the words "AE-related" so that the scope of pharmacogenetic research is better reflected.
- Section 9.1.1: updated to add that study treatment must be discontinued at RECIST 1.1 PD if it occurs when pembrolizumab was previously discontinued. Also, to remove previous provision for continuation of treatment until induction is complete for patients with squamous histology.
- Section 10.1.1.1 updated to replace the Adverse Event of Special Interest (AESI) name 'DILI (Hepatic transaminases and bilirubin elevations)' with the new AESI name 'Abnormal Liver Parameters'.
- Section 10.1.4 updated to add that if a pregnancy occurs while on study treatment, the newborn will be followed for at least 12 months.

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 2 (12-Jul-2019)

Amendment rationale

A total of 30 subjects were enrolled and treated in the safety run-in part. Enrollment for the safety run-in part was closed on 20-Mar-2019. The Recommended Phase 3 Regimen (RP3R) of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy has been determined and communicated to all investigators on 10-Jun-2019. Enrollment for the randomized part of the study started on 10-Jun-2019. As of 12-Jul-2019, 127 subjects have been screened and 25 subjects have been randomized.

The main objective of amendment 02 is:

- To clarify treatment beyond disease progression (PD):
- Any subject who presents with PD based on RECIST 1.1 prior to completion of the 4 cycles of induction treatment is allowed to complete the induction cycles (as long as canakinumab/matching placebo is not administered as single agent) if it is in the best interest of the subject, as determined by the investigator.
- Subjects with non-squamous histology who present with RECIST 1.1 PD during maintenance will be allowed to continue pemetrexed beyond PD if it is in the best interest of the subject, as determined by the investigator.
- Study treatment beyond iRECIST confirmed progression (iCPD) may be allowed if the investigator determines that it is in the best interest of the subject. In such cases, approval by a Novartis study physician is required.

In addition, the following changes are implemented:

- Update of exclusion criteria #5, #7 and #13 to ensure consistency with prior studies and based on advice received by the Steering Committee:.
- Exclusion criterion #5 is updated to allow subjects with known untreated, asymptomatic brain metastases (i.e. no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, no lesion >1.0 cm and a maximum of 3 lesions) to be enrolled.
- Exclusion criterion #7 is updated to allow subjects with history of auto-immune disease or known auto-immune disease who have not been treated with systemic therapy in the past 2 years before study entry to be enrolled in the study.
- Exclusion criterion #13 is updated to clarify that subjects with history of non-infectious pneumonitis who did not require steroids (grade 1) can be enrolled in the study. Subjects with history of (non-infectious) pneumonitis who required steroids or have current pneumonitis are excluded from the study.
- To clarify that subjects with a tumor of adenosquamous histology can be treated as either squamous or non-squamous histology, as per Section 6.3.2. The chemotherapy treatment selected must match the histology selected in the Interactive Response Technology (IRT) system at time of randomization (squamous or non-squamous).
- To add two circulating tumor DNA (ctDNA) sample collection time points (C8D1 and C12D1). The sequencing of specific gene panels and determination of mutation load will be performed using ctDNA. Therefore, the additional ctDNA sample collection time points will allow a better longitudinal follow up of the patients as well as the evaluation of liquid

biopsy as an early detection method of progression. In addition, this longitudinal analysis will allow the understanding of potential mechanisms of resistance to treatment.

- To clarify as requested per Chinese authorities, that the biomarker assessments are not to be done unless approval in China has been obtained by all relevant Chinese authorities. As of the release of this amendment, no site has been initiated and no subject has been screened or has been enrolled in this study in China.
- To remove reference to number of slides or blood volume needed for biomarker assessments, as these are already detailed in the Central Laboratory Flowchart. Reference to Flowchart was added.
- To clarify that use of steroids is allowed in case of immune-related adverse events (irAE) since these events can be caused by pembrolizumab.

Editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.

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.

- Protocol summary, Table 8-3 and Section 8.5.3: updated to clarify that biomarkers samples will not be done in China unless approval has been obtained by all relevant Chinese authorities.
- Figure 3-3, Table 4-1, section 6.1.4.1, Section 7, Table 8-4, Section 8.3.1.2 and Section 9.1.1: language updated from “pembrolizumab +/- canakinumab/matching placebo” to “study treatment”.
- Section 4: Table 4-1 language updated to clarify treatment beyond RECIST 1.1 PD and iCPD.
- Section 5.2: Exclusion criteria #5, #7 and #13 updated.
- Section 6.1.1.2: updated to clarify treatment of subjects with adenosquamous histology.
- Section 6.1.3: updated to clarify treatment beyond RECIST 1.1 PD. Also to clarify treatment with pemetrexed for subjects with non-squamous histology beyond disease progression.
- Section 6.1.4: added reference to section 6.1.4.1.
- section 6.1.4.1: updated to clarify study treatment beyond RECIST 1.1 PD and to add that in some cases study treatment beyond iCPD might be allowed. Also, to clarify treatment beyond disease progression when pembrolizumab has been discontinued for toxicity.
- Section 6.2.2.1: updated to clarify that use of steroids to treat immune-related adverse events is allowed.
- Section 6.3.2: updated to clarify stratification for subjects with adenosquamous histology.
- Section 6.5.3.1: language for adverse drug reactions simplified.
- Table 6-7: added footnote clarifying exceptions to general guidance for mandatory dose modification.
- Section 6.6.2: added clarification that investigator will provide study drug name (if available) in case of emergency unblinding, as requested by Italian Health Authority.

- Section 7: added clarification for study treatment beyond iRECIST iCPD.
- Section 8: Table 8-2 and Table 8-3 updated to add a footnote to clarify SAE data collection during safety follow up and to remove the footnote referring to number of slides required for biomarker assessments at screening. Table 8-3further updated to add two additional time points for ctDNA collection and a footnote to clarify biomarker assessments for China.
- Section 8.4.1: added clarification that a subject on-site visit may not be required and local laboratory testing is allowed for visits with safety laboratory assessments only.
- Section 8.5.3 updated to clarify biomarker assessments for China to include reference to Central Laboratory Flowchart.
- Section 8.5.3.1 and 8.5.3.3: updated to remove reference to number of slides or blood volume needed for biomarker assessments
- Section 9.1.1: updated to add study treatment discontinuation if RECIST 1.1 PD occurs when canakinumab/matching placebo is administered as a single agent. Also, to clarify study treatment discontinuation for subjects with squamous histology who discontinued pembrolizumab due to toxicity during induction and have RECIST 1.1 disease progression during induction
- Section 9.2: language on post-study treatment simplified.

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 1 (12-Dec-2018)

Amendment rationale

As of 12-Dec-2018, no site has been initiated. No subject has been screened and no subject has received study treatment.

The main objective of the amendment 01 is:

- To implement the Health Authority request to obtain subject informed consent before continuing with canakinumab/matching placebo as a single agent prior to disease progression by RECIST 1.1. A separate informed consent will be created to be signed by subjects who will receive canakinumab/matching placebo as single agent before disease progression per RECIST 1.1, per physician discretion, in case all other study drugs (pembrolizumab and chemotherapy) were permanently discontinued.

Additional main objectives for the amendment 01 are:

- To modify the tumor assessment frequency in the maintenance treatment phase, where the tumor assessments will be done "every 9 weeks through week 75" instead of "every 9 weeks (for the next 21 weeks)" and thereafter after week 75, it will be done every 12 weeks. This modification is aligned with the current protocol median PFS assumptions and will ensure that the targeted improvement in median PFS will be detected more accurately.
- To align the assessment schedule in the safety run-in part with the one in the randomized part of the study by adding safety assessments on Cycle 5 Day 1.

In addition, the following modifications have been implemented:

- Clarification of some inclusion/exclusion criteria and also modification of some of them in order to allow more flexibility for the enrollment/randomization
  - NSCLC staging was updated to be aligned with AJCC v.8
  - The inclusion criteria for lipase was changed from lipase < ULN to lipase ≤ 1.5x ULN (grade 1), since the criteria was considered to be too restrictive for enrollment of cancer patients
  - For subjects with squamous NSCLC molecular testing at screening (EGFR and/or ALK) are not required
  - A sub-bullet point has been added to clarify that patients with known ROS-1 rearrangement or BRAF V600 mutation will be excluded, if required by local guidelines.
  - Tuberculosis exclusion criteria was updated to clarify that the need for tuberculosis treatment should be based on local guidelines
  - Update of the interstitial lung disease/ pneumonitis exclusion criteria to only exclude cases of grade ≥ 2; in alignment with the exclusion used for pembrolizumab studies.
- Revision of the assessment schedules for the safety run-in and the randomized part of the study, by removing safety laboratory assessments (hematology and chemistry) of Day 15 on Cycle 5 and subsequent Cycles for subjects on pemetrexed, to reduce patient burden. There are country-specific local differences on how these assessments are managed when taking pemetrexed, thus the protocol guidance is that pemetrexed use is to be managed according to the locally approved label and local practice.

- Updates performed per Novartis Hepatoxicity Clinical safety Guideline (2018) for the Table 6-7 Criteria for mandatory dose interruption and re-initiation for canakinumab/matching-placebo for adverse drug reactions, the Section 6.5.4.2 Follow up on potential drug-induced liver injury (DILI) cases, and the Table 6-8 Guidance on specific clinical and diagnostic assessments has been added.
- Updated sentence in the section 10.1.1 Adverse events per regulatory requirement: "Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment".
- Updated Section 6.2.1.1.2 to add cautionary language regarding the use of concomitant therapies that are substrates of CYP450 enzymes with a narrow therapeutic index, as the use of canakinumab may reverse cytokine induced suppression of CYP450.

In addition, editorial revisions, clarifications and corrections are made throughout the protocol to improve consistency.

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.

- Protocol Summary, Tables 8-2, 8-3 and 8-4, Section 8.3.1.2: Modified the tumor assessment frequency in the maintenance treatment phase, where the tumor assessments will be done "every 9 weeks through week 75" instead of "every 9 weeks (for the next 21 weeks)" and thereafter after week 75, it will be done every 12 weeks.
- Section 1.1.1.1: mPFS abbreviation when describing KEYNOTE-189 results has been corrected to median PFS, correct number of patient randomized in the KEYNOTE-407 has been added and update on the pembrolizumab approval status included.
- Section 1.1.1.1: The reference for pemetrexed SmPC in European Union has been added.
- Section 1.1.1.1, 3, 4.1, 5.1: Revised NSCLC staging to align with AJCC v.8.
- Section 3: Number of the referenced sections has been corrected.
- Section 3: Figures 3-1 and 3-2: Number of the referenced sections has been corrected.
- Section 3: Figure 3-1: Updated to add pemetrexed per investigator's decision for non-squamous subjects only (Cohort C) in maintenance phase.
- Section 4.2.2: Figure 4-2: Title has been updated to reflect correct unit of hs-CRP level.
- Section 5.1: Inclusion criteria #9 laboratory value "serum lipase" updated to allow grade 1.
- Section 5.2: Exclusion criteria #3 specification for EGFR mutations has been updated to clarify mentioned examples are not limited to those.
- Section 5.2: Exclusion criteria #3 sub-bullet has been updated to clarify that molecular testing (EGFR and ALK) are not needed for subjects with pure squamous cell histology, and a sub-bullet point has been added to clarify that patients with known ROS-1 rearrangement or BRAF V600 mutation will be excluded, if required by local guidelines.

- Section 5.2: Exclusion criteria #8 has been updated to clarify the need for tuberculosis treatment to be based on local guidelines.
- Section 5.2: Exclusion criteria #13: History of interstitial lung disease or pneumonitis updated to exclude only cases of grade ≥ 2 in alignment with the exclusion used for pembrolizumab studies.
- Section 5.2: Exclusion criteria # 19: clarification brought to tubal ligation.
- Section 6.1.1.1: Tables 6-1, 6-2: Footnote added to clarify that pemetrexed can be continued for the non-squamous subjects after the induction cycles as determined by the investigator according to local approved label and local practice.
- Section 6.1.1.1: Table 6-3: Pemetrexed added in the table and footnote to clarify that pemetrexed for non-squamous subject can be started after the induction cycles as determined by the investigator according to local approved label and local practice.
- Section 6.1.1.3: Figures 6-1 and 6-2: Updated with correct the number of the sections referenced.
- Section 6.1.3: Updated to clarify that subjects with less than 4 cycles of induction treatment can also continue into maintenance treatment, that only subjects with non-squamous histology can receive pemetrexed in maintenance treatment and subjects with RECIST PD during induction can continue the maintenance with pembrolizumab +/- canakinumab (or canakinumab matching placebo) but without pemetrexed.
- Section 6.1.4: Updated to clarify when a subject can continue canakinumab/matching placebo treatment even if pembrolizumab and other study drugs have been discontinued due to unacceptable toxicity.
- Section 6.1.4: Added that a separate informed consent is to be signed by subjects who will receive canakinumab/matching placebo as single agent before disease progression per RECIST 1.1 (see rationale for main objectives for amendment 01).
- Section 6.1.4.1: Criteria for treatment beyond progression have been clarified .
- Section 6.2.1.1.2: Clarification on the use of CYP450 substrates with a narrow therapeutic index per Health Authority request.
- Section 6.2.1.1.2: Clarification on the use of warfarin or warfarin-like treatment with narrow therapeutic index. Text moved from section 6.2.1 to Section 6.2.1.1.2.
- Section 6.2.2.1: Updated to clarify that any antineoplastic therapy are not allowed from start to the end of study treatment.
- Section 6.5.1.2: Clarification on evaluability criteria for safety run-in subjects in case canakinumab dose is de-escalated to Q6W regimen
- Section 6.5.2: Pharmacodynamics (PD) removed from the criteria being looked at for the RP3R determination.
- Section 6.5.3: Updated to clarify pembrolizumab dosing in case chemotherapy needs to be interrupted due to toxicity.
- Section 6.5.3.1: Table 6-7: Updated with revised Novartis hepatoxicity clinical safety guidance.
- Section 6.5.4.2: Table 6-8: Added table detailing guidance on specific clinical and diagnostic liver assessments

- Section 6.5.4.2: Updated to include the revised DILI language per revised Novartis hepatoxicity clinical safety guidance.
- Section 6.7: Added information related to the instructions for use of canakinumab/matching placebo.
- Section 8: Table 8-1 (visit windows): Specific time window for physical examination and serum pregnancy test removed to simplify assessment scheduling. In addition updated to clarify that all safety follow-up assessments are applicable.
- Section 8: Table 8-2 (Assessment Schedule, Safety run-in part): Visit name "Prior/concomitant medications" row corrected by replacing the term "non-drug therapies" with "prior/concomitant medication".
- Section 8: Table 8-2 (Assessment Schedule, Safety run-in part): Safety assessments for Cycle 5 Day 1 added (see rationale for main objectives for amendment 01.
- Section 8: Table 8-2 (safety run-in part)and 8-3 (randomized part): Updated by removing safety laboratory assessments (hematology and chemistry) from Day 15 on Cycle 5 and subsequent cycles for subjects on pemetrexed (see rationale for main objectives for amendment 01).
- Section 8: Tables 8-2 (safety run-in part) and 8-3 (randomized part): Pregnancy test and footnotes updated to clarify that screening assessments are to be done for all female subjects and post-baseline only for women with child-bearing potential.
- Section 8: Table 8-2 (safety run-in part) and 8-3 (randomized part): Antineoplastic therapies since discontinuation of study treatment updated to specify the assessment to be done during follow up period.
- Section 8: Table 8-3 (randomized part): Brain CT or MRI specification updated to align with Table 8-2 and 8-4.
- Section 8: Table 8-3 (randomized part), Section 8.5.1: Updated to state ePROs will be completed on Day 1 of each cycle, at EOT, + 7 and +28 days post confirmed RECIST 1.1 PD, and during efficacy follow up (for subjects who discontinue study treatment for reasons other than RECIST 1.1 PD).
- Section 8: Table 8-3 (randomized part): Drug administration updated to specify timepoints for subjects on nab-paclitaxel only.
- Section 8: Table 8-3 (randomized part): Updated Cycle 1 Day 2 to reflect updated PK sampling.
- Section 8: Table 8-3 (randomized part): Updated by adding Cycle 2 Day 2 to reflect updated PK sampling.
- Section 8: Table 8-3 (randomized part): Footnote for hs-CRP updated to guide reader to the corresponding subsection for more details.
- Section 8.2: Updated to clarify that serum pregnancy testing is for all female subjects at screening. Definition of vital signs was added per Health Authority request.
- Section 8.4.1: Table 8-5: Updated to include "pancreatic amylase (as needed)".
- Section 8.4.4: Updated to clarify ECG assessments may be taken any time pre-dose, not required to be taken within 20 minutes of PK collection.

- Section 8.4.5: Updated to clarify the serum and urine pregnancy test frequency for women of child bearing potential.
- Section 8.5.1: Clarification added on ePRO (Patient Reported Outcome) data collection.
- Section 8.5.2: Table 8-7: Updated to specify and simplify frequency of the PK blood sampling of chemotherapy drugs in order to reduce patient burden.
- Section 8.5.3: Clarification on the methodology of the blood collection for biomarker sample.
- Section 8.5.3.2: Updated to clarify that biomarker results will be blinded and won't be communicated to the investigational sites.
- Section 9.2: Updated to clarify the strategy of final analysis in the CSR for safety run-in.
- Section 10.1.1: Updates to add the exception of the related progressive disease reported as a SAE and update to remove redundancies.
- Section 12: Updated to clarify when the final analysis of the study data for safety run-in will be reported in the CSR.
- Section 12.1.3: Clarification on the minimum exposure criterion for safety run-in subjects in case canakinumab dose is de-escalated to Q6W regimen.
- Section 12.7: Modify $p<0.00001$ values for the 1st interim OS boundaries to reflect the exact p-values in decimals.
- Section 15: Some references have been updated.
- Section 16.2: Updated to include the new version of the "Guidelines for iRECIST".
- Section 16.3.1.3: Updated to remove duplication.
- Section 16.5: Appendix 5 "Medications to be used with caution with canakinumab while on the study", Table 16-19 was added to list CYP450 substrates with a narrow therapeutic index.
- Section 16.7: Appendix 7: Table 16-20 "Dose modifications Guidelines for Pembrolizumab drug related Adverse Events" has been fully revised

The protocol summary has been updated to reflect the changes throughout the document as well as the list of abbreviations, the glossary of terms.

At last, minor editorial changes (e.g. typographical mistakes, grammatical changes, rewording) to improve flow and consistency, and correction of spelling errors or typographical errors, have been made throughout the protocol.

IRB Section

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 Consents. Sites are required to update and submit for approval revised Informed Consents that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CACZ885U2301
Full Title	A randomized, double-blind, placebo-controlled, phase III study evaluating the efficacy and safety of pembrolizumab plus platinum-based doublet chemotherapy with or without canakinumab as first line therapy for locally advanced or metastatic non-squamous and squamous non-small cell lung cancer subjects (CANOPY-1)
Brief title	Study of efficacy and safety of pembrolizumab plus platinum-based doublet chemotherapy with or without canakinumab in previously untreated locally advanced or metastatic non-squamous and squamous NSCLC subjects
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug
Study type	Interventional
Purpose	To evaluate the efficacy, safety and pharmacodynamics of canakinumab versus canakinumab matching-placebo in combination with pembrolizumab and platinum-based doublet chemotherapy in NSCLC.
Rationale	The rationale for treating subjects with canakinumab is based upon the key role inflammation plays in the development and spread of NSCLC and the ability of canakinumab to suppress elevated C-reactive protein (CRP), which correlates with NSCLC stage. CANTOS, a cardiovascular study demonstrated that not only was the composite endpoints of stroke and myocardial infarction decreased by canakinumab, but also the occurrence of and mortality from NSCLC was decreased. Additionally, CRP suppression correlated with responses in NSCLC patients treated with atezolizumab.
Primary Objective(s)	**Safety run-in part:** • To determine the recommended Phase 3 dose regimen (RP3R) of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy. **Double-blind, randomized, placebo-controlled part:** • To compare progression free survival (PFS) between the two treatment arms • To compare overall survival (OS) between the two treatment arms.
Secondary Objectives	**Safety run-in part:** • To characterize the pharmacokinetics of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy • To characterize the safety and tolerability of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy • To characterize the immunogenicity (anti-drug antibodies) of canakinumab and pembrolizumab • To assess the preliminary clinical anti-tumor activity (overall response rate, disease control rate and duration of response) of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy **Double-blind, randomized, placebo-controlled part:** • To evaluate overall response rate (ORR), disease control rate (DCR), time to response (TTR) and duration of response (DOR) • To characterize the safety profile of the two treatment arms. • To characterize the pharmacokinetics of canakinumab, pembrolizumab and chemotherapy • To characterize the immunogenicity (anti-drug antibodies, ADA) of canakinumab and pembrolizumab. • To assess PROs in the two treatment arms
Study design	**Safety run-in part**

	This is an open label part to determine RP3R of canakinumab in combination with pembrolizumab and platinum-based doublet chemotherapy. **Double-blind, randomized, placebo controlled part** This is a double-blind, randomized, placebo-controlled part to evaluate the efficacy and safety of canakinumab vs. canakinumab matching-placebo in combination with pembrolizumab plus platinum-based doublet chemotherapy followed by maintenance therapy. **Open label extension phase** This is an open label extention (OLE) phase. If OS reaches statistical significance at one of the interim or final analyses, all subjects still on treatment or in safety/efficacy follow up will transition to the OLE phase, following unblinding of investigational sites to treatment allocation. If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, OLE will be initiated after final OS analysis, following the unblinding of investigational sites. Subjects will transition to a reduced study assessment schedule. Subjects randomized to canakinumab matching-placebo will be given the opportunity to cross over to canakinumab if the investigator determines this is in the subject's best interest and per subject discretion provided they fulfill crossover criteria. Post implementation of protocol amendment 05, subjects will transition into an assessment schedule aligned to standard of care with their current treatment and dosing regimen.
Population	The study will include adult subjects with locally advanced or metastatic NSCLC Approximately 27 subjects up to 54 subjects, in case next dose regimen level should be assessed, will be enrolled in the safety run-in part and approximately 600 subjects will be randomized in a 1:1 ratio (approximately 300 subjects in each treatment arm) in the double-blind, randomized, placebo-controlled part.
Key Inclusion criteria	• Histologically confirmed locally advanced or metastatic NSCLC • Measurable disease by RECIST 1.1 • Known PD-L1 status • ECOG performance status (PS) 0 or 1
Key Exclusion criteria	• Previous immunotherapy or treatment with IL-1β inhibitor. • Subjects with epidermal growth factor receptor (EGFR) sensitizing mutations and/or anaplastic lymphoma kinase (ALK) rearrangement • History of severe hypersensitivity reaction to monoclonal antibodies, platinum containing drugs, nab-paclitaxel, paclitaxel, pemetrexed or any known excipients of these drugs.

Study treatment	**Safety run-in part:**
	Canakinumab 200 mg s.c. injection in combination with pembrolizumab 200 mg i.v. infusion and platinum-based doublet chemotherapy:
	• **Cohort A (for non-squamous):** carboplatin AUC 5 mg/mL*min i.v. infusion plus pemetrexed 500 mg/m2 i.v. infusion
	• **Cohort B (for non-squamous):** cisplatin 75 mg/m2 i.v. infusion plus pemetrexed 500 mg/m2 i.v. infusion
	• **Cohort C (for squamous or non-squamous):** carboplatin AUC 6 mg/mL*min i.v. infusion plus paclitaxel 200 mg/m2 i.v. infusion
	Double-blind, randomized, placebo-controlled part
	• **Investigational treatment arm**: canakinumab 200 mg s.c. injection (Q3W) in combination with pembrolizumab 200 mg i.v. infusion (Q3W) and platinum-based doublet chemotherapy (Q3W):
	  • **For non-squamous**: carboplatin AUC 5 mg/mL*min i.v. infusion or cisplatin 75 mg/m2 plus pemetrexed 500 mg/m2 i.v. infusion
	  • **For squamous**: carboplatin AUC 6 mg/mL*min i.v. infusion plus paclitaxel 200 mg/m2 or nab-paclitaxel 100 mg/m2 i.v. infusion

	• **Control treatment arm**: canakinumab matching-placebo s.c. injection in combination with pembrolizumab 200 mg i.v. infusion and platinum-based doublet chemotherapy (same as for the investigational treatment arm). Note: subjects with adenosquamous histology can be treated as either squamous or non-squamous histology; see Section 6.3.2. The chemotherapy treatment selected must match the histology selected in the IRT system at time of randomization (squamous or non-squamous). **Open label extension phase** Subjects enrolled in the safety run-in and subjects randomized to the canakinumab arm in the randomized part will transition into the OLE with their current treatment and dosing regimen. Subjects randomized to the canakinumab matching-placebo arm in the randomized part will be allowed to cross over to canakinumab (in combination with the other study drugs), per investigator and subject discretion provided they fulfill crossover criteria (Section 6.1.3). Post implementation of protocol amendment 05, subjects will transition into an assessment schedule aligned to standard of care with their current treatment and dosing regimen.
Efficacy assessments	• **Radiological tumor assessments** by investigator (RECIST 1.1 and immune RECIST): At screening and every 6 weeks for the first 12 weeks, then every 9 weeks (through week 75) and every 12 weeks thereafter Note: In OLE, the same tumor assessment schedule as in safety run-in (SRI) and randomized part will be followed until 159 weeks (approximately 3 years) after the study Cycle 1 Day 1; thereafter, every 24 weeks. • **Survival phone calls**: every 12 weeks after safety and efficacy follow-up period Post implementation of protocol amendment 05, the efficacy follow-up and survival follow-up will no longer be collected.
Safety assessments	• Physical examination • ECOG performance status, body weight and vital signs • Laboratory assessments, including hematology, biochemistry, coagulation, thyroid function, hepatitis testing and urinalysis • Pregnancy tests for women of child-bearing potential (serum pregnancy test at screening for all women) • Electrocardiogram (ECG) • Adverse events (AEs) the severity, the relationship with to study treatment and the seriousness Post implementation of protocol amendment 05, coagulation, thyroid function, hepatitis testing, urinalysis and ECOG performance status will no longer be collected.
Other assessments	• Pharmacokinetics of canakinumab, pembrolizumab, carboplatin, cisplatin, paclitaxel, nab-paclitaxel and pemetrexed • Immunogenicity (ADA) of canakinumab and pembrolizumab • Pharmacodynamics (PD) IL-1β and PD biomarkers* (including hs-CRP, hs-IL-6) • Patient reported outcomes (PROs) assessments by the European Organization for Research and Treatment of Cancer quality of life (EORTC QLQ-C30 and EORTC QLQ-LC13) and EuroQoL (EQ-5D-5L) questionnaires *For China only: biomarker tests will not be done unless approval has been obtained by all relevant Chinese authorities. Post implementation of protocol amendment 05, all assessments listed above will be stopped.
Data analysis	**Safety run-in part - Identification of recommended regimen** The primary analysis will be conducted when at least 6 evaluable subjects (among approximately 9 subjects enrolled) in each of the 3 treatment cohorts have been observed for dose limiting toxicity (DLT) for the first 42 days. A lower recommended regimen may be explored based on other safety and PK data from the current study (Section 6.5.1.2) **Bayesian adaptive approach**

	The determination of RP3R will be guided by a Bayesian analysis of DLT data for each cohort for the first 42 days (6 weeks) during which subjects receive the combination of canakinumab pembrolizumab plus platinum-based doublet chemotherapy. The relationship between dose and the probability of DLT is modeled using logistic regression. Details of the Bayesian logistic regression model (BLRM) are given in Section 16.3 . The dose limiting toxicity (DLT) relationship of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy is modeled by a BLRM for each dose regimen that comprises single agent toxicity parts and interaction part. Single agent toxicity is modeled using logistic regression for the probability of a subject experiencing a DLT against log-dose. The odds of a DLT for each dose regimen are then calculated **Starting dose** The starting dosing regimen are the following (Section 6.5.1.1): • Cohort A: canakinumab 200 mg Q3W in combination with pembrolizumab 200 mg, carboplatin AUC 5 mg/mL*min and pemetrexed 500 mg/m2 Q3W • Cohort B: canakinumab 200 mg Q3W in combination with pembrolizumab 200 mg, cisplatin 75 mg/m2 and pemetrexed 500 mg/m2 Q3W • Cohort C: canakinumab 200 mg Q3W in combination with pembrolizumab 200 mg, carboplatin AUC 6 mg/mL*min and paclitaxel 200 mg/m2 Q3W. For this starting dose level of canakinumab (i.e. 200 mg Q3W), the prior risk of excessive toxicity is 15%, 10%, and 22% for cohorts A, B, and C, respectively, which satisfies the escalation with overdose control (EWOC) criterion. **Dose recommendation** Dosing regimen decisions are guided by the EWOC principle. A dosing regimen may only be used for newly enrolled subjects if the risk of excessive toxicity at that dosing regimen is < 25% (Rogatko et al 2007). **Double-blind, randomized, placebo-controlled part** **Progression free survival (PFS)** Assuming a proportional hazards model for PFS, the null hypothesis will be tested at one-sided 1% level of significance. If OS is statistically significant at either interim or final analysis, then the 1.5% alpha assigned to OS will be transferred to PFS and PFS will be tested at one-sided 2.5% level of significance (Section 12.4) In the primary analysis, PFS will be tested using the log-rank test stratified by randomization stratification factors when approximately 253 PFS events are observed. The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS and PFS rate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arms. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI based on the Wald test. **Overall survival (OS)** Assuming a proportional hazards model for OS, the null hypothesis will be tested at one-sided 1.5% level of significance. If PFS by investigator assessment per RECIST1.1 is statistically significant at 1% level of significance, then the 1 % alpha assigned to PFS will be transferred to OS and OS will be tested at one-sided 2.5% level of significance (Section 12.4). In the primary analysis, OS will be tested using the log-rank test stratified by randomization stratification factors. The distribution of OS will be estimated using the Kaplan-Meier method. The median OS and OS rate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arms. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of OS, along with 95% CI based on the Wald test. Secondary endpoints (overall response rate (ORR), disease control rate (DCR), time to response (TTR) and duration of response (DOR)) will be also presented by treatment group (Section 12.5.1) **Open Label Extension (OLE) phase**

	Any additional data for ongoing subjects in the randomized part following the primary OS analysis and data for subjects in OLE (if initiated) will be further summarized in a final study report.
Key words	ACZ885, canakinumab, pembrolizumab, carboplatin, cisplatin, paclitaxel, nab-paclitaxel, pemetrexed, NSCLC, squamous, non-squamous, hs-CRP, IL-1β, PD-L1, CANOPY

1 Introduction

1.1 Background

1.1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1.1 Background on NSCLC and use of immunotherapy

An estimated 1.8 million people were diagnosed globally with lung cancer in 2012 and there were 1.6 million deaths from this disease (Globocan 2012). The number of new lung cancer cases is expected to grow by about 70% over the next 2 decades (Globocan 2012). Non-small cell lung cancer (NSCLC) accounts for 85% of the lung cancer diagnoses and approximately 70% of patients present with advanced disease (Molina et al 2008). The majority of subjects present with advanced disease; only 25-30% of subjects have surgically resectable disease and only half of these resected subjects are disease-free at 5 years (Molina et al 2008, Maeda et al 2010, American Community Survey 2012). Surgery is the treatment of choice for subjects with NSCLC stages I through IIIA. Subjects with stage IIIB, IIIC and IV NSCLC without targetable oncogenic drivers are usually treated with chemotherapy with the option of surgery and/or radiotherapy; however, patients with known alterations (such as EGFR, ALK, B-Raf proto-oncogene; BRAF, or c-ros oncogene 1; ROS-1) are candidates for targeted treatments (NCCN v1. 2018)

The first-line standard-of-care for locally advanced and metastatic NSCLC patients without a targetable oncogenic driver is pembrolizumab in combination with platinum-based doublet chemotherapy. In the United States (US), pembrolizumab is approved in the first-line setting in non-squamous NSCLC as a single agent (PD-L1 expression in tumor of $\geq$ 50%) and in combination with platinum-based doublet chemotherapy. The median overall survival of these patients treated with platinum–based doublet chemotherapy is only 8-10 months, with approximately 50-70% of patients having disease stabilization or tumor shrinkage in response to first-line chemotherapy (Schiller et al 2002, Scagliotti et al 2002, Scagliotti et al 2008). Although there are differences in toxicity, cost, schedule and convenience; clinical advantage of any platinum-based doublet chemotherapy regimens is trivial.

Maintenance therapy is used in non-squamous NSCLC treatment to prolong response to therapy for patients responding or whose disease is stable after first-line therapy. Maintenance can be categorized into switch-maintenance (the maintenance therapy is different from the first line) or continuation therapy (one of the components of the first line is continued in the maintenance phase). Currently, pemetrexed is the only compound formally approved for maintenance therapy of non-squamous NSCLC in US (Alimta®USPI 2004) and European Union (EU) (Alimta®SmPC 2009).

Immunotherapy has further shaped the treatment landscape of advanced NSCLC patients, both in the pretreated and treatment-naive setting. Monoclonal antibodies targeting PD-1 and PD-L1 (nivolumab, durvalumab, pembrolizumab, and atezolizumab) have each demonstrated significant activity as monotherapy and superiority over single agent chemotherapy in pretreated NSCLC either PD-L1 selected or unselected and have been recently approved by the Health Authorities in this setting (Barlesi 2016, Langer et al 2016, Antonia et al 2017).

Pembrolizumab currently requires PD-L1 testing in some countries for use in approved indications (e.g. United States and Japan).

Nivolumab is approved in many countries for patients who have previously received chemotherapy for both squamous and non-squamous lung cancer on the basis of two randomized phase III trials (Borghaei et al 2015, Brahmer et al 2015) that demonstrated superior OS for nivolumab over docetaxel in both squamous and non-squamous NSCLC. In the first-line setting, nivolumab was not superior to platinum-based doublet chemotherapy in patients with PD-L1 ≥ 1% based on the CheckMate 26 study (Carbone et al 2017). A second study, CheckMate-227, demonstrated PFS improvement of the combination of nivolumab+ipilimumab over chemotherapy in patients with high tumor mutational burden NSCLC (regardless of PD-L1 levels) (Hellmann et al 2018).

Atezolizumab was also approved for previously treated NSCLC with progression on or following a platinum-containing regimen based on superior OS over docetaxel chemotherapy (Rittmeyer et al 2017) regardless of the PD-L1 expression and of the histology.

In first-line treatment for non-squamous advanced NSCLC patients, atezolizumab in combination with bevacizumab plus platinum based chemotherapy demonstrated PFS benefit over bevacizumab plus chemotherapy (Reck et al 2016), with an improvement in OS (Socinski et al 2018) regardless of PD-L1 expression and EGFR or ALK genetic aberration. Additionally, these studies did not demonstrate any significant OS or PFS benefit in this setting between the additions of either atezolizumab or bevacizumab to a platinum based chemotherapy. In first-line treatment of squamous NSCLC the addition of atezolizumab to carboplatin plus nab-paclitaxel in a phaseIII trial, IMpower 131, demonstrated a PFS benefit and the OS data is still awaited (Jotte et al 2018).

Pembrolizumab is also approved in many countries for the treatment of advanced NSCLC after platinum-based doublet chemotherapy in patients whose tumor have PD-L1 expression on ≥1% of tumor cells on the basis of KEYNOTE-010 study (Herbst et al 2016). Here the median overall survival was significantly longer for each of the pembrolizumab arms over the docetaxel and the OS benefit was consistent across all histologies. In first-line NSCLC treatment, pembrolizumab was initially approved as monotherapy for NSCLC patients whose tumor have a PD-L1 expression ≥50% based on the results of KEYNOTE-024 (Reck et al 2016) that demonstrated superiority of pembrolizumab over platinum-based doublet chemotherapy in the first-line setting. More recently, pembrolizumab was approved in combination with platinum-based doublet chemotherapy in non-squamous NSCLC as first line treatment in KEYNOTE-189 (Gandhi et al 2018): patients were to receive either four cycles of pembrolizumab or matching placebo + chemotherapy (pemetrexed + carboplatin or cisplatin) followed by pembrolizumab or matching placebo + pemetrexed maintenance. The pembrolizumab containing arm compared to chemotherapy significantly prolonged median Progression Free Survival (mPFS): 8.8 vs. 4.9 months, HR=0.52 (95% CI: 0.43 to 0.64, p<0.001) regardless of PD-L1 status (Gandhi et al 2018). In addition, overall survival (OS) was prolonged at 12 months: 69.2% versus 49.4%, HR=0.49 (95% CI: 0.38 to 0.64, p<0.001). The results of KEYNOTE-407 in first-line squamous NSCLC (Paz-Ares 2018), 559 patients were randomized to receive either pembrolizumab in combination with carboplatin plus taxane or placebo in combination with carboplatin plus taxane for four cycles followed by maintenance therapy with pembrolizumab or placebo until disease progression. The pembrolizumab arm was statistically

significantly superior for the primary endpoints of PFS and OS (median PFS (6.4 months versus 4.8 months, HR 0.56, 95% CI: 0.45 to 0.70, p<0.0001) and median OS (15.9 months versus 11.3 months, HR 0.64, 95% CI: 0.49 to0.85, p=0.0008)) and for the secondary endpoint, overall response rate 58.4% versus 35.0%, p=0.0004). All PD-L1 tumor cell expression subgroups experienced similar benefit (<1%, 1%-49%, ≥ 50 %). Based on the results of study KEYNOTE-189, the combination of pembrolizumab and chemotherapy is approved in the EU and US in the first line setting for metastatic non-squamous NSCLC. Additionally, the combination of pembrolizumab and chemotherapy is approved in the US in the first-line setting for metastatic squamous NSCLC based on the results of KEYNOTE-407.

Taken together, the addition of an immune checkpoint blocker to platinum-based doublet chemotherapy over chemotherapy alone leads to an improvement in efficacy, regardless of histologic subtype or PD-L1 status (Herzberg et al 2017). However, PFS and OS remain short and highlight the need for additional therapeutic options. Based on the body of evidence pembrolizumab in combination with standard platinum-based doublet chemotherapy is an appropriate control and therefore will be used as a comparator arm for the study.

1.1.1.2 The role of inflammation and IL-1β in NSCLC

Chronic inflammation plays an important role in the development of NSCLC. Key etiological risk factors such as smoking (Bracke et al 2006), second-hand smoke exposure, chronic infections, and exposure to environmental toxins cause a chronic inflammatory milieu that plays a critical role in carcinogenesis, particularly, in lung cancer (Krysan et al 2008, O'Callaghan et al 2010).

The cytokine interleukin-1β (IL-1β) is one of the mediators of pulmonary inflammation that promotes lung cancer. Genetic evidence also links IL-1β to lung cancer risk (Bhat et al 2014). Polymorphisms in the promoter region of the IL-1 gene result in altered levels of IL-1β expression and are associated with an increase in lung cancer risk (Li and Wang 2013). Extensive preclinical data supports the role of IL-1β in several distinct steps in carcinogenesis. These steps include tumor initiation, promotion, angiogenesis, and metastasis (O'Byrne et al 2000, O'Byrne and Dalgleish 2001, Dalgleish and O'Byrne 2006, Mantovani et al 2008). Tumor initiation is the first step in carcinogenesis and involves the acquisition of mutations in normal cells that allow a selective growth advantage. IL-1β is thought to create a microenvironment that promotes tumor initiation (Wu et al 2016). In a mouse model of tumor initiation, the genetic loss of IL-1β resulted in an attenuation of 3-methylcholanthrene (MCA)-induced tumor formation (Krelin et al 2007, Voronov et al 2010). The ability of IL-1β to promote tumor initiation is thought to be mediated through the induction of Nuclear Factor Kappa Beta (NF-κB) expression (Kasza 2013). The second step in carcinogenesis is tumor promotion. This step is characterized by the growth of a primary tumor from a single transformed cell. This step is mediated in part by tumor associated macrophages (TAM) and cytokines that these TAMs produce, such as tumor necrosis factor alpha (TNFα), IL-6, and IL-1β (Becker 2006). The third step in carcinogenesis is angiogenesis, in which blood vessel formation is induced to generate a vascular network for the primary tumor. In this process, IL-1β is thought to play a critical role, as tumors in mice deficient in IL-1β failed to induce vascular endothelial growth factor (VEGF) expression and tumor angiogenesis (Apte et al 2006). The final step in carcinogenesis is metastasis. IL-1β is thought to play an important role in this step as well via the induction of genes critical for invasion and cell

adhesion. Using a mouse model of lung cancer metastasis, Yano and colleagues demonstrated that tumors genetically programmed to express high levels of IL-1β developed lung metastasis more rapidly than controls, with treatment with an anti-IL-1β antibody inhibited formation of lung metastasis (Yano et al 2003). Taken together, these results suggest an important role for IL-1β in multiple steps of carcinogenesis.

Activation of the inflammation and elevated levels of CRP have been shown to negatively impact several components of the immune system (Chaturvedi et al 2010). Mature IL-1β can promote the infiltration of immunosuppressive cells into the tumor microenvironment, including myeloid derived suppressor cells (MDSCs) and TAMs (Guo et al 2014). Elevated CRP levels, induced by the expression of IL-1β and IL-6, have also been shown to directly and negatively impact the immune cell environment. Both *in vitro* and transgenic mouse models have demonstrated the ability of CRP to suppress the differentiation and proliferation of T-cells, and inhibit the maturation, migration and function of dendritic cells (Frenzel et al 2007, Zhang et al 2015, Jimenez et al 2018). Moreover, a shift towards increased number of suppressive MDSCs was demonstrated in a human CRP expression mouse model (Pegues et al 2016). Taken together, these findings indicate a role for CRP/IL-1β towards a more immunosuppressive microenvironment, contributing to immune evasion and tumor progression. Counteracting these effects through inhibition of the CRP/IL-1β axis may result in a microenvironment more susceptible to IO agents such as anti-PD-(1) inhibitors used in combination. To this end, recently reported results from the atezolizumab in second and third line NSCLC studies demonstrated that decreases in CRP correlated with RECIST 1.1 responses, prolonged PFS and OS for atezolizumab but not docetaxel treated subjects (Patil et al 2018).

Given the evidence for the importance of IL-1β signaling in carcinogenesis, treating cancer with IL-1β blockade has been proposed (Wu et al 2016, Jenkins 2017).

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

1.1.2.1 Canakinumab in NSCLC

Canakinumab (ACZ885) is a high-affinity human anti-interleukin-1β (IL-1β) monoclonal antibody that belongs to the Immunoglobulin G1 (IgG1)/κ isotype subclass. Canakinumab is manufactured in a murine SP2/0 cell line. Currently canakinumab is approved and marketed as Ilaris® for the treatment of IL-1β driven auto-inflammatory diseases: gouty arthritis, Still's disease, Cryopyrin Associated Periodic Syndromes (CAPS), Systemic Juvenile Idiopathic Arthritis (SJIA), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF). IL-1β, a proinflammatory cytokine, is a key mediator of atherosclerotic plaque formation and the atherothrombotic process.

The secondary prevention of major adverse cardiovascular events (MACE, a composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke in patients with a history of MI and inflammatory atherosclerosis) was investigated in the CANTOS (**C**anakinumab **AN**ti-inflammatory **T**hrombosis **O**utcomes **S**tudy) study. In this randomized, placebo-controlled study with 10,061 patients with a history of prior myocardial infarction and inflammatory atherosclerosis and elevated hs-CRP at baseline were enrolled and were treated with either

placebo or 50, 150 or 300 mg s.c. every three months. The administration of canakinumab demonstrated a clinically and statistically significant effect in reducing the risk of MACE. Since treatment with immune suppression in transplant medicine and in rheumatic disorders has been found to cause cancers (Turesson and Matteson 2013, Geissler 2015), a safety analysis in CANTOS to evaluate the development of cancer as an adverse event was included as a prespecified analysis. This analysis showed that canakinumab reduced the occurrence of lung cancer and lung cancer mortality compared to placebo in a dose-dependent manner (Ridker et al 2017). The median hs-CRP at baseline for patients who were subsequently diagnosed with cancer was 6.0 mg/L. Canakinumab treatment also resulted in dose-dependent decrease in hs-CRP of 26-41% and IL-6 decrease of 25-43%; lung cancer incidence was less frequent in the treated groups that was dose dependent (Ridker et al 2017). Lung cancer mortality was significantly less in the canakinumab 300 mg treated group than in the placebo group (HR=0.23 [95% CI 0.10-0.54]) and in the pooled canakinumab patients (p=0.0002 for trend across all active-treated patients) (Ridker et al 2017). Total cancer mortality was significantly lower in the pooled canakinumab groups versus the placebo group (p=0.0007), but only the 300 mg every 12 weeks canakinumab group had statistically significant lowering (HR=0.49, 95% CI: 0.31-0.75, p=0.0009). All-cause mortality did not differ significantly between the canakinumab and placebo groups, HR=0.94 (95% CI; 0.83-1.06) (Ridker et al 2017). Circulating tumor deoxyribonucleic acid (DNA) was detected at baseline in 66% (44/67) of lung cancer patients from CANTOS, suggesting that these patients may have had pre-existing cancer at baseline.

One hypothesis to explain the lower lung cancer incidence and lower lung cancer mortality is that canakinumab reduced the rate of progression, invasiveness and metastatic spread of already existing tumors, which were too small to be detected at study entry (Ridker et al 2017). This data along with the preclinical information that IL-1β supports tumorigenic inflammation provides the rationale to investigate the therapeutic role of canakinumab. The dose of canakinumab to be given in this current study, 200 mg s.c. every 3 weeks, was selected by PK modeling simulations and available human safety data (Section 4.2).

Table 1-1 Canakinumab characteristics

Chemical name:	**Recombinant human monoclonal antibody ACZ885**
INN:	canakinumab
Proprietary name:	ILARIS®
Drug class:	Anti-inflammatory
Laboratory code:	ACZ885

For further details on canakinumab, especially on non-clinical pharmacokinetics and drug metabolism, non-clinical pharmacology and toxicology, please refer to Section 4 of the current [canakinumab IB].

1.1.2.2 Pembrolizumab in NSCLC

Pembrolizumab (Keytruda®) is a monoclonal humanized antibody designed to identify and block the PD-1 receptor. By blocking PD-1, the T-cells can “find” and destroy the cancer cells. Pembrolizumab is approved for the treatment of advanced NSCLC (Section 1.1.1.1) (Herbst et al 2016, Reck et al 2016, Langer et al 2016, Gandhi et al 2018, Paz-Ares 2018).

1.1.2.3 Pembrolizumab and canakinumab combination

There are no data available defining the recommended doses of pembrolizumab and canakinumab when given in combination. No drug-drug interaction is expected between pembrolizumab and canakinumab (Section 1.1.3) and full doses of both drugs (200 mg i.v. Q3W for pembrolizumab and 200 mg s.c. Q3W for canakinumab) will be used as the starting doses based on the ongoing study CPDR001X2103 which used 600 mg s.c. Q8W as the expansion dose for canakinumab and 400 mg i.v. Q4W as the dose for PDR001, a PD-1 inhibitor under development (Section 4.2.4). Data available from this study showed no excess toxicity with the combination canakinumab and PDR001 was observed, with the AE profile of the combination being representative of the individual AE profiles of each compound (Section 4.2.4). The safety profile of PDR001 is similar to other PD-(L)1 inhibitors.

1.1.3 Potential for drug-drug interactions

1.1.3.1 Canakinumab in combination with chemotherapeutic agents and in combination with pembrolizumab and chemotherapy

Specific studies to investigate drug-drug interactions (DDI) have not been conducted with canakinumab. Given canakinumab is a therapeutic monoclonal antibody, it is expected to be catabolized into amino acids by general protein degradation process and is not anticipated to be directly eliminated through hepatic/renal metabolism and excretion to compete with the elimination of the majority of the platinum-based doublet chemotherapy agents studied in this trial, which are mainly eliminated through metabolism and renal excretion. Therefore, the risk of DDI between canakinumab and chemotherapeutic agents is anticipated to be low. DDI potential between canakinumab and pembrolizumab is also considered to be low given both antibodies are eliminated by non-metabolism dependent pathway.

Antibodies that modulate cytokines, which may regulate cytochrome P450 (CYP450) enzymes, may cause DDI with small molecule drugs because of the potential to alter CYP-mediated metabolism (Harvey and Morgan 2014). Anti-cytokine antibodies such as canakinumab that target and neutralize these proinflammatory cytokines or their receptors are capable of restoration of CYP450 enzymes to normal levels (Ashino et al 2007). However, since most of the platinum-based doublet chemotherapeutic agents (except for paclitaxel and nab-paclitaxel) are not eliminated by CYP, the risk of DDI between canakinumab and platinum-based doublet chemotherapy agents is anticipated to be low. Conversely, the platinum-based doublet chemotherapy agents are not expected to affect canakinumab clearance, which is mainly governed by protein catabolism pathways.

1.1.3.2 Pembrolizumab

Similar to canakinumab, since pembrolizumab is cleared from the circulation through protein catabolism, no metabolic DDI is expected. Nevertheless, PK of pembrolizumab will be characterized in this study, so that DDI, if any, between pembrolizumab, canakinumab and chemotherapeutic agents in this trial, can be explored. The use of systemic corticosteroids or immunosuppressants before starting pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

1.1.3.3 Chemotherapeutic agents

Except for paclitaxel and nab-paclitaxel, none of the chemotherapeutic agents have major CYP enzyme involvement and are primarily eliminated by the kidney. The metabolism of paclitaxel/nab-paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel or nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4 (Section 6.2.1.1.2).

PK of platinum-based doublet chemotherapy agents, in addition to canakinumab and pembrolizumab, will be characterized in this study, so that the DDI, if any, between these drugs can be explored. As chemotherapeutic agents (paclitaxel, nab-paclitaxel, cisplatin, carboplatin, and pemetrexed) are intended to be used in combination with canakinumab and pembrolizumab in this study, this evaluation is particularly important since chemotherapeutic agents have narrow therapeutic range (FDA Guidance 2012).

1.2 Purpose

The purpose of this multicenter, randomized, double-blind, placebo-controlled phase III study is to evaluate the efficacy and safety of canakinumab vs. canakinumab matching-placebo in combination with pembrolizumab in addition to 4 cycles of platinum-based doublet induction chemotherapy, followed by maintenance therapy in subjects with the overall response of stable disease (SD) or better after completion of induction therapy, in subjects with locally advanced stage or metastatic NSCLC. The double-blind, randomized, placebo-controlled part will be preceded by a safety run-in part where the recommended dose of the combination of canakinumab with pembrolizumab plus platinum-based doublet chemotherapy will be confirmed.

As of 25-Oct-2021 study CACZ885U2301 did not meet the primary endpoints of PFS and OS at final analysis. Canakinumab combined with pembrolizumab plus platinum doublet chemotherapy did not improve PFS and OS, when compared to placebo in the first line treatment of subjects with advanced/metastatic NSCLC without ALK or EGFR aberrations. Prespecified thresholds for statistical significance between arms were not crossed (for PFS: HR = 0.85 [95% CI: 0.67, 1.09]; one-sided stratified log-rank test p = 0.102; and for OS: HR = 0.87 [95% CI: 0.70, 1.10]; one-sided stratified log-rank test p = 0.123). The median PFS and OS were 6.77 (95% CI: 5.62, 7.75) and 20.83 months (95% CI: 16.26, Non Estimable) in the canakinumab arm, respectively; and 6.77 (95% CI: 5.52, 6.93) and 20.17 months (95% CI: 16.23, 22.37) in the placebo arm, respectively.

Potential canakinumab benefit trends were reported in some subgroups. No differences were reported in the secondary endpoints (ORR, DCR, DOR). The median TTR was not reached in either arm and the probability of TTR at 6 months was comparable between arms.

The overall safety and tolerability profile observed in this study with the combination of canakinumab, platinum-based chemotherapy and pembrolizumab as of 30-Jun-2023 was as expected and consistent with the known safety profile of each agent. No new safety signals or unexpected safety findings were identified with study treatment. The observed adverse events were as expected in this patient population and clinically manageable.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• **Safety run-in part:** To determine the RP3R of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy	• Incidence of dose limiting toxicities in the first 42 days of study treatment
• **Double-blind, randomized, placebo-controlled part:** To compare PFS by local investigator assessment as per RECIST1.1 and OS between the two treatment arms.	• PFS based on local investigator assessment as per RECIST 1.1 and OS are multiple primary endpoints
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• **Safety run-in part:** To assess the preliminary clinical anti-tumor activity (overall response rate, disease control rate and duration of response) of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy.	• ORR, DCR, DOR by local investigator's assessment according to RECIST 1.1
• **Safety run-in part:** To characterize the safety and tolerability of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy.	• Type, frequency and severity of adverse events and reactions, changes in laboratory values, vital signs, ECGs
• **Safety run-in part:** To characterize the pharmacokinetics of canakinumab in combination with pembrolizumab plus platinum-based doublet chemotherapy.	• Concentration and PK parameters of canakinumab, pembrolizumab and chemotherapy
• **Safety run-in part:** To characterize the immunogenicity (anti-drug antibodies) of canakinumab and pembrolizumab	• Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment of canakinumab and pembrolizumab
• **Double-blind, randomized, placebo-controlled part:** To evaluate overall response rate (ORR), disease control rate (DCR), time to response (TTR) and duration of response (DOR) by local investigator assessment per RECIST 1.1 in the treatment arms.	• ORR, DCR, TTR and DOR based on local investigator assessment as per RECIST 1.1
• **Double-blind, randomized, placebo-controlled part:** To characterize the safety profile of the two treatment arms.	• Frequency of adverse events, serious adverse events, AEs leading to treatment discontinuation, proportion of patients with laboratory abnormalities, ECG, and vital signs.
• **Double-blind, randomized, placebo-controlled part**: To characterize the pharmacokinetics of canakinumab, pembrolizumab and chemotherapy.	• Concentration and PK parameters of canakinumab, pembrolizumab and chemotherapy
• **Double-blind, randomized, placebo-controlled part**: To characterize the immunogenicity (anti-drug antibodies, ADA) of canakinumab and pembrolizumab.	• Anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment of canakinumab and pembrolizumab
• **Double-blind, randomized, placebo-controlled part**: To assess PROs (EORTC QLQ-C30 with the QLQ-LC13 lung cancer module and EQ-5D-5L) including symptoms, physical functioning and health-related quality of life in the two treatment arms.	• Time to definitive 10-point deterioration symptom scores for chest pain, cough and dyspnea per QLQ-LC13 questionnaire as three primary PRO variables of interest and time to definitive deterioration in global health status/QoL, shortness of breath and pain per QLQ-C30 as secondary PRO variables of interest.

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• **Double-blind, randomized, placebo-controlled part**: To assess the relationship between PK of canakinumab, and PD biomarkers, safety and efficacy.	• Canakinumab PK by inflammatory markers (e.g. hs-CRP and hs-IL-6), safety (e.g. AEs and laboratory abnormalities) and efficacy (PFS and OS).
• **Double-blind, randomized, placebo-controlled part**: To assess the predictive and prognostic value of baseline levels of blood-based and tissue-based biomarkers on efficacy .	• PFS and OS by biomarkers at baseline
• **Double-blind, randomized, placebo-controlled part:** To explore iPFS, iORR, iDCR based on iRECIST as per local investigator in the two treatment arms.	• iPFS, iORR and iDCR based on iRECIST criteria as determined by investigator
• **Double-blind, randomized, placebo-controlled part**: To explore the long term benefit intermediate to PFS and OS by assessing PFS2 in the two treatment arms.	• PFS2
• **Double-blind, randomized, placebo-controlled part**: To characterize the impact of immunogenicity (anti-drug antibodies, ADA) on PK, safety and efficacy.	• Antidrug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment vs PK, AEs, lab abnormalities and efficacy endpoints (PFS, OS)

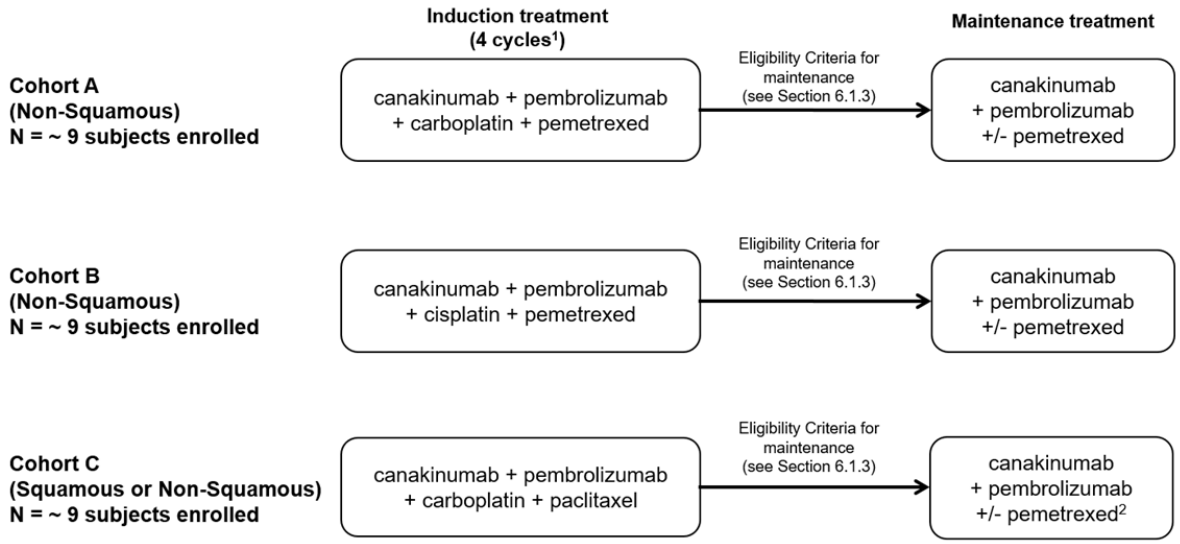
3 Study design

This is a double-blind, randomized, multicenter phase III study evaluating the efficacy and safety of canakinumab vs. canakinumab matching-placebo in combination with pembrolizumab in addition to 4 cycles of platinum-based doublet induction chemotherapy, followed by maintenance therapy in subjects with AJCC v. 8 stage IIIB/IIIC (not eligible for definite chemoradiation therapy) or stage IV (metastatic) NSCLC regardless of PD-L1 levels and histology (squamous and non-squamous). Subjects who completed 4 cycles of induction treatment and fulfill eligibility criteria as defined in Section 6.1.3 will enter the maintenance treatment phase. For dosing regimen, please refer to Section 6.1.1 .

This is a 2-part study:

Part 1: Safety run-in part The safety run-in part will determine the recommended regimen of canakinumab (recommended Phase 3 dose regimen, RP3R) in combination with pembrolizumab and platinum-based doublet chemotherapy. Approximately 9 subjects will be enrolled in each cohort to get at least 6 evaluable subjects (for evaluability definition refer to Section 6.5.1.2), as described in below Figure 3-1 . For choice of chemotherapy medications and dosing regimen please refer to Section 6.1 and Section 6.1.3 .

Figure 3-1 Part 1: Safety run-in, study design



1 1 cycle = 3 weeks, 2 for Non-Squamous subjects only

Part 2: Double-blind, randomized, placebo-controlled part

Once the RP3R for canakinumab in combination with pembrolizumab and platinum-based doublet chemotherapy is confirmed in the safety run-in part, the double-blind, randomized, placebo-controlled part of the study will open.

The randomization will be stratified based on PD-L1 status (Tumor Proportion Score (TPS) <1% vs. ≥1%), geographic region (East Asia **vs.** North America + Western Europe **vs.** Rest of the world) and histology (squamous vs. non-squamous). PD-L1 unevaluable subjects will be included with the TPS <1% group. Approximately 600 subjects will be randomized in a 1:1 ratio to two treatment arms as described in below Figure 3-2 .

No cross-over treatment from canakinumab matching-placebo treatment arm to canakinumab treatment arm will be allowed.

Open Label Extension (OLE) phase

If OS reaches statistical significance at one of the interim or final analyses, all subjects on treatment or in safety/efficacy follow up will transition to the open label extension (OLE) phase following unblinding of investigational sites to treatment allocation. If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, OLE will be initiated after final OS analysis, following the unblinding of investigational sites. Subjects will transition to a reduced study assessment schedule, as specified in Table 8-4.

Subjects enrolled in the safety run-in part and subjects randomized to the canakinumab arm in the randomized part will transition into the OLE phase with their current treatment and dosing regimen (Section 6.1.1.3).

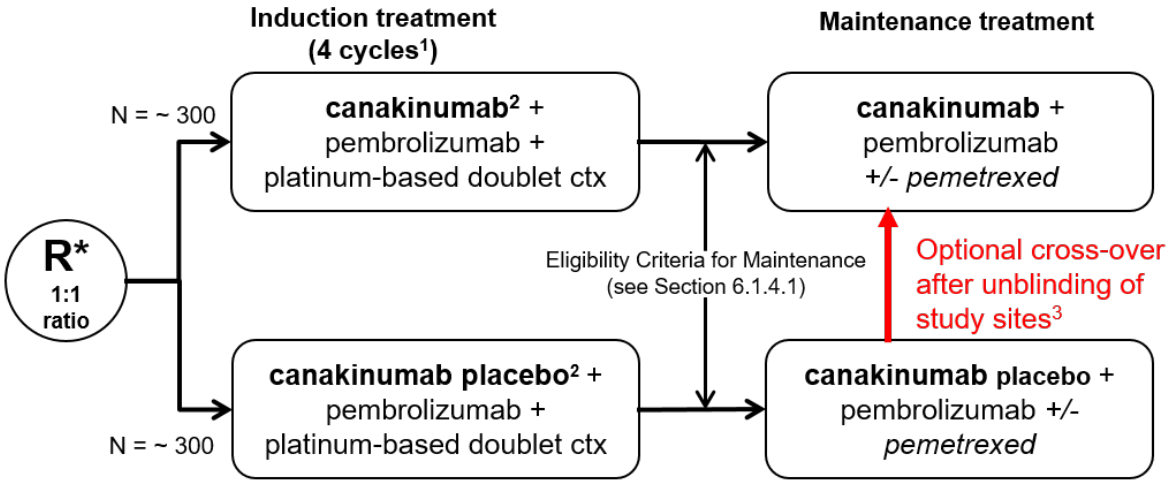
Subjects randomized to the canakinumab matching-placebo arm in the randomized part will be allowed to cross over to canakinumab if the investigator determines this is in the subject's best interest and per subject discretion, provided they fulfill crossover criteria (Section 6.1.3).

Subjects should cross over to canakinumab in combination with the other study drugs, i.e. pembrolizumab and maintenance chemotherapy, where applicable. Crossover is optional; subjects who do not wish to cross over to canakinumab will transition into the OLE phase with the other study drugs (Section 6.1.1.3).

Any enrolled or randomized subjects who have already discontinued study treatment and are in efficacy and/or safety follow-up will also transition into the OLE and follow the reduced study assessment schedule, as specified in Table 8-4.

Subjects in survival follow-up will not transition into OLE and will continue survival follow-up as specified in Table 8-2 and Table 8-3. All subjects in OLE will be followed up for 5 years from the time of last subject first treatment in the randomized part or until all subjects discontinue the study treatment and complete their safety follow up, die, withdraw consent or are lost to follow up, whichever happens first.

Figure 3-2 Part 2: Double-blind, randomized, placebo-controlled, study design, including optional crossover during the OLE phase

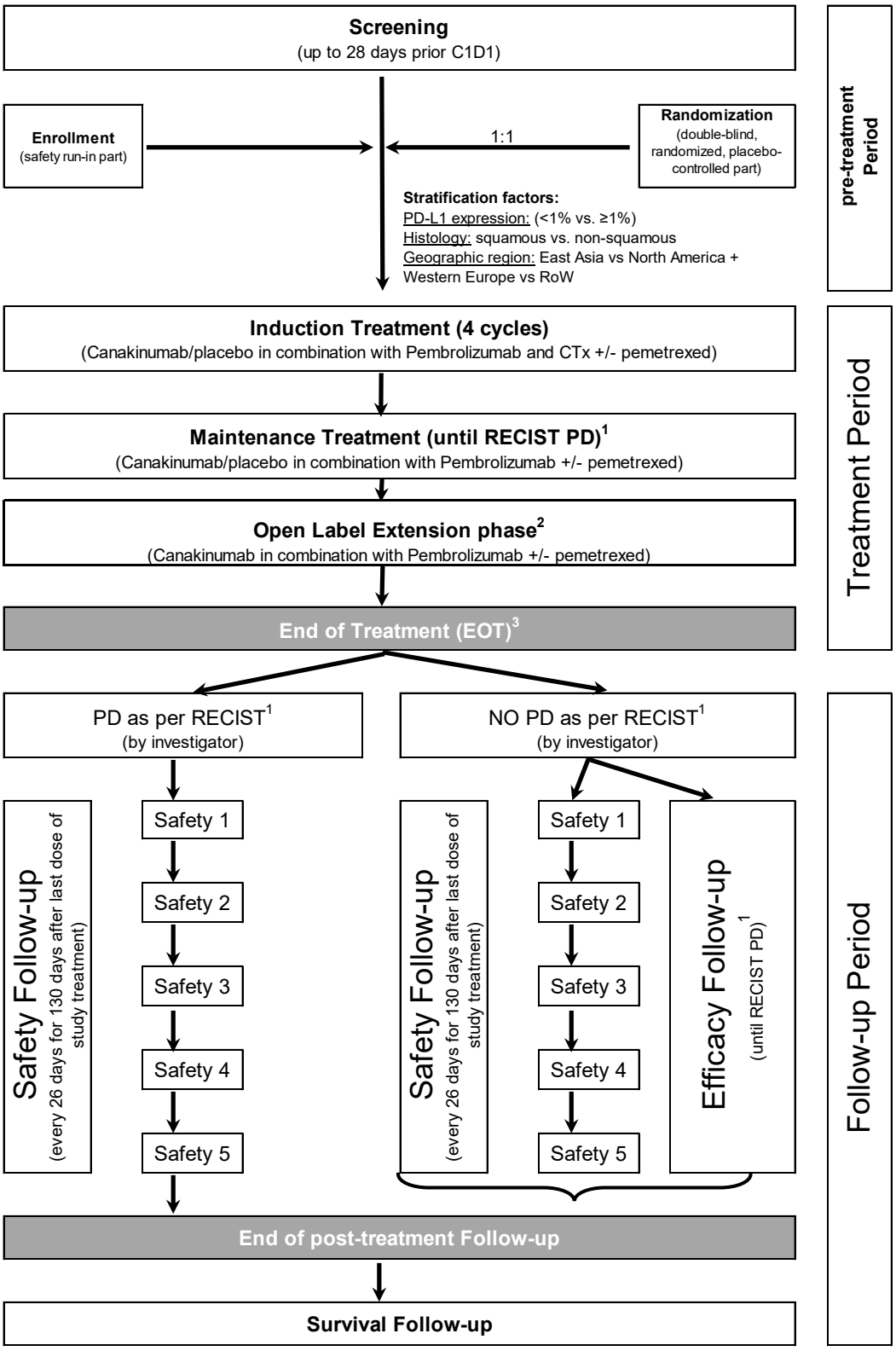


*Stratification factors:
- PD-L1 expression: (<1% vs. ≥1%) -> by Novartis designated laboratory
- Histology: squamous vs. non-squamous
- Geographic region: East Asia vs North America + Western Europe vs RoW

[1] cycle = 3 weeks; [2] canakinumab/matching-placebo at RP3R; CTx = chemotherapy; R = Randomization. [3]Applicable during the OLE phase. OLE phase was never implemented since the study did not meet its primary endpoints of Overall Survival (OS) and Progression Free Survival (PFS) at final analysis.

After treatment discontinuation, all subjects (enrolled in part 1 or randomized in part 2) will enter in the safety follow-up period and in an efficacy follow-up (as applicable) and then in a survival follow-up as described in the study flow Figure 3-3. Post implementation of protocol amendment 05, all subjects who discontinue study treatment will enter or complete the safety follow-up and the subjects in efficacy or survival follow-up will discontinue the study. For further details, please refer to study completion and post-study treatment Section 9.2.

Figure 3-3 Study flow



[1]For subjects who continue study treatment beyond RECIST 1.1 PD as per investigator, tumor assessments will be done until immune confirmed PD (iCPD) as per iRECIST per investigator or discontinuation of study treatment, whichever occurs first. CTx = Chemotherapy. [2]OLE will be initiated following unblinding of investigational sites if OS reaches statistical significance at one of the interim or final analyses. If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, OLE will be initiated after final OS analysis following unblinding of investigational sites. [3]Post implementation of protocol amendment 05, all subjects who discontinue study treatment will be followed for safety assessments for 130 days post EOT

4 Rationale

As described in Section 1.1.1.2 , chronic inflammation plays an important role in the development of cancer (Dalgleish and O'Byrne 2006, Mantovani et al 2008, Bhat et al 2014). CRP is an inflamatory marker that has been associated with a higher risk of developing lung cancer (Chaturvedi et al 2010). CRP has also been shown to be elevated in NSCLC and correlates with tumor size and stage, and points to poor outcome and prognosis (Aref H and Refaat 2014).

CRP is a downstream target of IL-1β and is therefore often used as a surrogate marker for IL-1β inhibition (Ridker 2016).

Countering the elevated activities of IL-1β pathway could potentially reduce the occurrence of lung cancer and lung cancer mortality a hypothesis that was corroborated by data from the CANTOS study (Section 1.1.2.1)

High CRP levels were associated with inferior Overall Survival after Immunotherapy (OSI) in lung cancer patients treated with nivolumab (Naqash AR 2017); these data support the hypothesis that inhibition of the IL-1β may lead to a microenvironment more susceptible to anti-PD-(1) inhibitors used in combination. Furthermore, recent pooled data from the atezolizumab studies in second and third line NSCLC patients demonstrated that decrease in CRP levels correlated with RECIST 1.1 responses and prolonged PFS and OS in the atezolizumab-treated arm (Patil et al 2018).

Taken together, these data reinforce the importance of inflammation as a target in cancer treatment and support the hypothesis that canakinumab, an IL-1β inhibitor, may synergize with PD-(L)1 inhibitors in the treatment of advanced or metastatic NSCLC. Given the positive results of pembrolizumab in combination with chemotherapy in first-line NSCLC , the current study (CACZ885U2301) is designed to evaluate the safety and efficacy of canakinumab in combination with pembrolizumab and platinum-based doublet chemotherapy to test this hypothesis.

4.1 Rationale for study design

The study will compare the addition of canakinumab to pembrolizumab plus platinum-based doublet chemotherapy as first line treatment for stage IIIB/IIIC (locally advanced) or stage IV (metastatic) NSCLC. The safety run in part establishes the RP3R and the safety profile for the canakinumab combination and is followed by a double blind randomized placebo controlled trial to determine the efficacy of adding canakinumab to the current standard of care. Stratification factors based on PD-L1 expression, histologic subtype and geographic region balances the predictive and prognostic factors. The double blind placebo controlled design minimizes the bias in the assessments of efficacy, safety and PROs.

Rationale for study design features is described in Table 4-1 .

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Randomization stratification factors: • PD-L1 expression (<1% vs. ≥1%) • Histology (squamous vs. Non-squamous) • Geographic region	The stratification factors have been selected to balance potential predictive and/or prognostic factors between the two arms: • PD-L1 expression has been shown to correlate with response to checkpoint inhibitors. This has been further confirmed by results from KEYNOTE-189, where the least benefit was observed in subjects with PD-L1 expression <1% (Gandhi et al 2018). Hence, randomization is stratified based on PD-L1 expression based on a 1% cut-off threshold. • Although anti-PD-1/PD-L1 activity is observed in both squamous and non-squamous histology, the magnitude of benefit and the absolute outcomes may differ slightly in the two histologies (Brahmer et al 2015, Borghaei et al 2015, Herbst et al 2016, Reck et al 2016, Herzberg et al 2017), therefore randomization is stratified based on disease histology. • Geographic region (East Asia **vs.** North America + Western Europe **vs.** Rest of the world) to account for possible differences in standard of care.
No treatment cross-over from canakinumab matching-placebo to canakinumab arm after disease progression as per RECIST 1.1 will be allowed.	This is to reduce confounding due to cross-over in OS outcome (primary objective)
Study treatment beyond initial disease progression by RECIST 1.1 will be permitted if it is in the best interest of the subject per physician discretion (details in Section 6.1.4.1). Canakinumab as single agent after RECIST 1.1 progression is not allowed. Study treatment will be discontinued upon confirmation of progression (iCPD) as per iRECIST. Note: Treatment beyond iRECIST confirmed progression (iCPD) may be allowed if considered to be in the best interest of the subject by the investigator. In such cases, approval by a Novartis study physician is required .	This is to ensure that those subjects who derive clinical benefit from study treatment (are clinically stable, tolerate the treatment and have no confirmed PD by immune response criteria (iCPD by iRECIST)) can continue to receive treatment. Timely follow-up after the initial PD will ensure that subjects with confirmed/rapid progression will be discontinued and can initiate adequate subsequent therapies. Continuation of study treatment will be allowed after RECIST 1.1 progression and until iCPD by iRECIST if the investigator assesses that the subject is deriving clinical benefit. Note that pembrolizumab treatment will be given for a maximum of 35 administrations (4 administrations of induction + 31 administrations of maintenance as per Keynote 189 study; Gandhi et al 2018)
Open Label Extension phase (OLE): if OS reaches statistical significance at one of the interim or final analyses, all subjects will transition to the open label extension (OLE) phase following unblinding of investigational sites to treatment allocation. If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, Subjects will transition to a reduced study assessment schedule. Subjects randomized to canakinumab-matching placebo will be allowed to cross over to canakinumab, as per investigator	The OLE phase will allow: • Subjects who continue to derive clinical benefit from the treatment, based on the investigator's evaluation, to continue to receive trial treatment. • Subjects in the placebo arm to receive added benefit from canakinumab treatment • A reduced schedule of assessments

Study Design Aspect	Rationale
and subject discretion, provided they fulfill crossover criteria. Crossover is optional.	
Post implementation of protocol amendment 05, subjects will continue with an assessment schedule aligned to standard of care. The efficacy follow-up and survival follow-up will no longer be collected. All subjects who discontinue study treatment will enter or complete the safety follow-up and the subjects in efficacy or survival follow-up will discontinue the study.	Protocol Amendment 05 will allow subjects to continue the study with a safety and efficacy assessment schedule aligned to to standard of care.

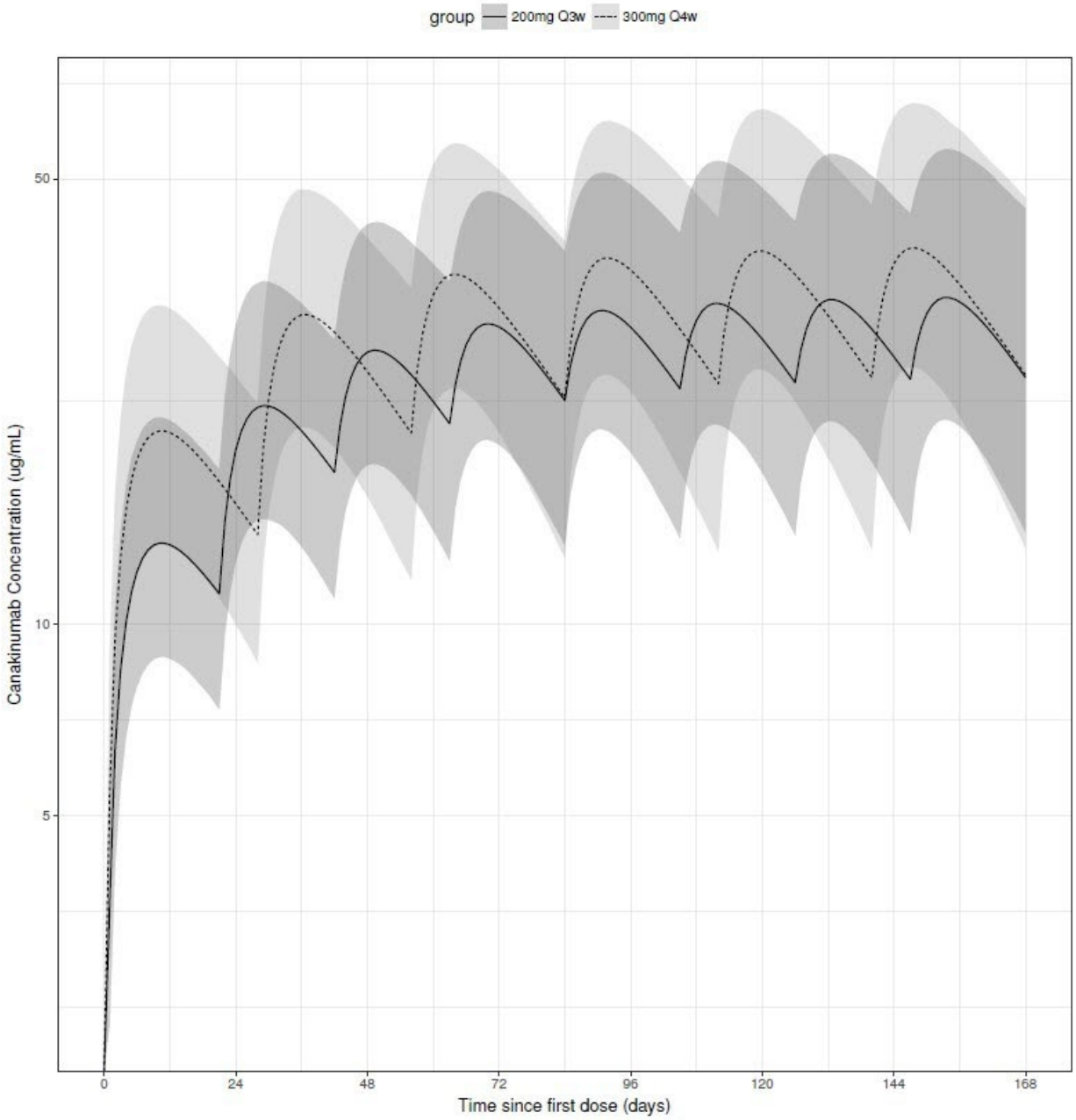
4.2 Rationale for dose/regimen and duration of treatment

In the safety run-in part, canakinumab dose will start at 200 mg every three weeks (Q3W) which is the dosing regimen selected for the development program in NSCLC. This dosing regimen is chosen on the basis of the pharmacokinetic (PK) and pharmacodynamics (PD) properties of canakinumab, the observed safety, biomarker and efficacy data from the CANTOS study, and the safety data from completed and ongoing canakinumab studies.

4.2.1 Pharmacokinetics (PK) consideration

Canakinumab displays PK properties typical of an IgG1 antibody, with a mean terminal half-life of 26 days (Ilaris® USPI). Every 3 weeks dosing schedule of canakinumab is feasible based on its half-life of 26 days, and its ability to suppress CRP for at least 1 month as previously demonstrated in two single-dose phase II studies with dose ranges of 0.03 to 10 mg/kg i.v. and 25 to 300 mg s.c. (Study [CACZ885A2213] in diabetes and Study [CACZ885H2251] in gouty arthritis). Population PK analysis and simulation were also performed to compare the steady-state PK of 200 mg Q3W versus 300 mg Q4W. 300 mg Q4W was selected as reference for comparison, because it is the highest approved regimen for canakinumab. As shown in Figure 4-1 , the simulated PK profiles of canakinumab at 200 mg Q3W and 300 mg Q4W are comparable, indicating that the safety margin with the 200 mg Q3W regimen is expected to be in line with the one from the currently approved regimen of 300 mg Q4W. Specifically, the maximum plasma concentration (Cmax) of 200 mg Q3W is not exceeding that of 300 mg Q4W.

Figure 4-1 Simulated PK profiles of canakinumab 200 mg Q3W s.c. and 300 mg Q4W s.c.



Line and band: median of individual simulated concentrations with 2.5-97.5% prediction interval. Values reported are median (solid line) and the 95% prediction interval (shaded area, 2.5th-97.5th percentile).

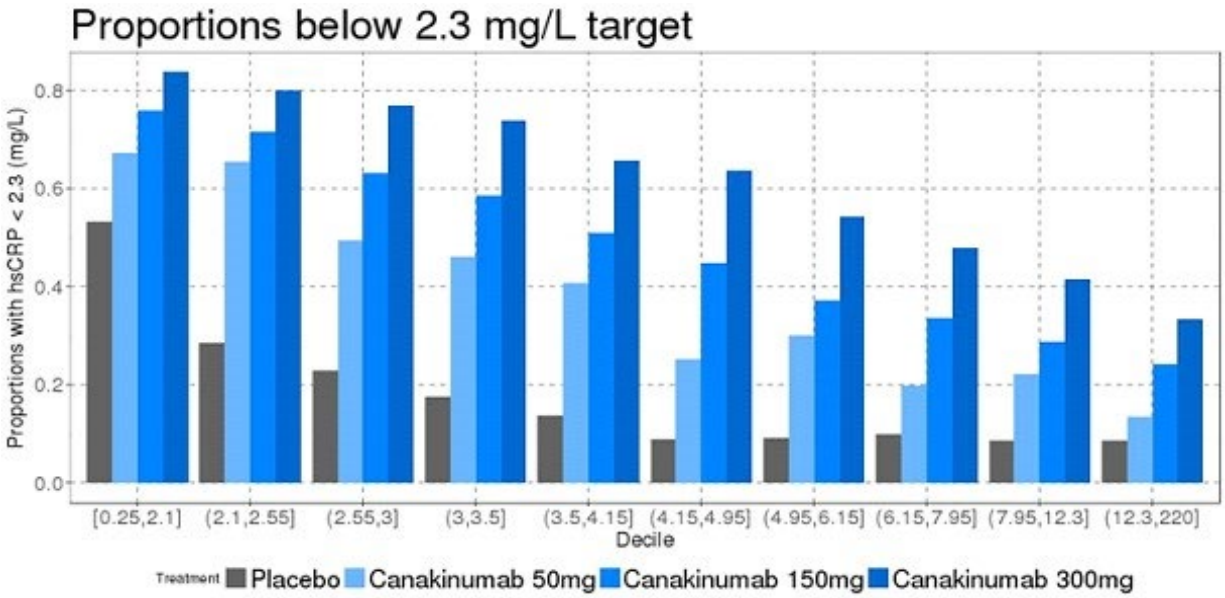
4.2.2 Efficacy and pharmacodynamics (PD) considerations

CANTOS study evaluated whether IL-1β inhibition might alter cancer occurrence and mortality as there is a strong inflammatory component to certain cancers, especially lung cancer. The results show that canakinumab, as compared to placebo, was associated with dose-dependent risk reductions in lung cancer and lung cancer mortality. There is a clear differentiation in

clinical benefits across all three dosing regimens, with the greatest risk reduction in lung cancer mortality achieved with the highest dose, 300 mg s.c. every three months. Hazard ratios (95% confidence interval, P-value) were 0.67 (0.37-1.20, P=0.18), 0.64 (0.36-1.14, P=0.13), and 0.23 (0.10-0.54, P=0.0002) for the 50 mg, 150 mg, and 300 mg s.c. dose groups, respectively as reported by (Ridker et al 2017). The dose-dependent pattern of hs-CRP reduction among subjects with lung cancer is also aligned with the clinical results, with the 300 mg group demonstrating the largest magnitude of reduction, relative to the other two treatment groups and placebo, with no saturating effect at 300 mg s.c. every three months.

The different median baseline hs-CRP levels among canakinumab-treated subjects in CANTOS who were subsequently diagnosed with cancer compared to those who did not (median 6.0 mg/L [Interquartile Range (IQR): 3.5-11.5 mg/L] versus 4.2 mg/L [IQR: 2.8-7.1 mg/L], P<0.0001) (Ridker et al 2017) likely reflect the different inflammatory status and risk for cancer. Notably, for subjects with higher baseline hs-CRP, the proportion of subjects with hs-CRP normalized to post-treatment target level (2.3 mg/L) is less, compared to subjects with lower baseline hs-CRP (Figure 4-2). This finding suggests that raising the dose and/or shortening the dosing interval which will increase canakinumab steady-state PK may lead to better control of inflammation in subjects with higher baseline hs-CRP and deliver greater efficacy in subjects with higher baseline hs-CRP. Publications examining hs-CRP levels in NSCLC subjects show that higher hs-CRP levels is correlated with higher stage and poor prognosis (Alifano et al 2011, Hara et al 2010, Vaguliené et al 2011).

Figure 4-2 Proportions of subjects with hs-CRP < 2.3 mg/ L by baseline hs-CRP declines in all subjects from the CANTOS study



Median hs-CRP at 3 months was 2.3 mg/L based on all subjects in the Full Analysis Set.

4.2.3 Safety considerations

The combination of canakinumab + pembrolizumab + pemetrexed for subjects with non-squamous NSCLC is expected to be administered at full dose of each of the drugs as no additive toxicity is anticipated from this triple combination based on the following rationale:

- the combination of pembrolizumab + chemotherapy is well tolerated at full doses used in the phase III trials, KEYNOTE-189 trial (Gandhi et al 2018) and KEYNOTE 407 (Paz-Ares 2018)
- the combination of PDR001 + canakinumab was well tolerated at full doses of each component in the ongoing Phase Ib study, [CPDR001X2103]. Hence, it is expected the combination of pembrolizumab + canakinumab will also be well tolerated;
- the main toxicities related to canakinumab administration possibly overlapping with pemetrexed are infection and neutropenia. These two side effects were however of low added frequency as compared to placebo in the CANTOS study.

The safety of combination of canakinumab at 200 mg s.c. Q3W with pembrolizumab + carboplatin + pemetrexed, pembrolizumab + cisplatin + pemetrexed and pembrolizumab + carboplatin + paclitaxel will be evaluated in the safety run-in part. The resulting canakinumab regimen will be used in the double-blind, randomized, placebo-controlled part of the study.

Overall, canakinumab safety and tolerability findings across the three dosing regimens in CANTOS showed no new or unexpected signals and are similar to that reported in other populations, which shows a well-tolerated safety profile following a wide range of dosing regimens [canakinumab Investigator's Brochure]. There were no meaningful differences between any of the canakinumab treatment groups and placebo in the overall incidence of AE or of serious adverse events (SAEs) in CANTOS. Based on ~ 570 subjects treated with canakinumab in interventional trials in approved indications, the most frequently reported adverse drug reactions (ADRs) were infections, predominantly of the upper respiratory tract. Majority of the events were mild to moderate, although serious infections were observed. Early recognition of infection symptoms and immediate use of antibiotics with appropriate measures can prevent serious outcome of infections. No neutralizing antibodies have been detected so far (Ilaris®, SmPC-2017).

As described in the canakinumab IB across the completed and ongoing studies, higher canakinumab doses (4 mg/kg [max. 300 mg] s.c. Q4W, 300 mg s.c. Q2W or 600 mg i.v. loading dose plus 300 mg s.c. Q2W) have been used before for other indications. These studies did not reveal clinically relevant differences in the types and severity of reported adverse events across different dose groups. The AEs observed were mostly mild and moderate in severity, and similar to that of the placebo group.

4.2.4 Consideration for combination with pembrolizumab and chemotherapy

Several canakinumab trials are ongoing in oncology: in particular, canakinumab is being evaluated in subjects with advanced NSCLC in an ongoing phase Ib study, [CPDR001X2103]. The rationale for the choice of the doses of canakinumab is also based on the outcomes of a phase Ib study (CPDR001X2103) where the combination of spartalizumab (PDR001, a PD-1 inhibitor from Novartis) and canakinumab are being evaluated. Available data on pharmacology, pharmacokinetics, and safety suggest that PDR001 behaves similarly to other approved PD-L1 inhibitors. In study [CPDR001X2103], a review of the safety and tolerability data showed that canakinumab at 600 mg s.c. Q8W is safe to be combined with PDR001 administered at 400 mg i.v. Q4W (Recommended Phase 2 Dose, RP2D) (refer the safety summary details in the next paragraph). Based on preliminary population PK simulation, 600 mg s.c. Q8W canakinumab

generates steady-state Cmax greater than that attained at the 200 mg s.c. Q3W; PDR001 at 400 mg i.v. Q4W is also expected to achieve steady-state exposure similar to those of pembrolizumab at 200 mg i.v. Q3W [PDR001 Investigational Brochure]. Therefore, no unexpected safety issues are expected with the administration of pembrolizumab in combination with canakinumab.

Overview of combination of PDR001 and canakinumab

Data for the combination of canakinumab is available from Study [CPDR001X2103], a Phase Ib study to characterize the safety, tolerability and pharmacodynamics of PDR001 in combination with CJM112, EGF816, canakinumab, or trametinib. As of the data cut-off (31-Jul-2017), 16 patients were enrolled and treated in the dose escalation part of the study, using three dose levels: 100 mg canakinumab s.c. Q8W (n=6), 300 mg canakinumab s.c. Q8W (n=7) and 600 mg canakinumab s.c. Q8W (n=3), all in combination with 400 mg Q4W PDR001. Fifteen patients (94%) experienced AEs of any grade, regardless of causality. The most common AEs were decreased appetite (6 patients, [37%]), fatigue (5 patients, [31%]), anemia and dyspnea (each in 4 patients, [25%]), and back pain, dizziness and nausea (each in 3 patients, [18%]). The majority of AEs were Grade 1/2. Six (37%) experienced AEs of any grade, suspected to be related to study treatment. The most frequent AEs suspected to be related to study treatment were fatigue (5 patients, [18%]) and decreased appetite (2 patients, [12%]). Seven patients (44%) experienced Grade 3/4 AEs regardless of causality. No patient had a Grade 3/4 AE that was suspected to be related to study treatment. Eight SAEs have been reported for 5 (31%) patients: Large Intestinal Obstruction, Urinary Tract Infection, Cystitis, Herpes Zoster, Lipase Increased (LT/Grade 4), Cancer Pain, Intercostal Neuralgia, Acute Respiratory Failure (LT/Grade 4). All 8 SAEs were assessed as not suspected of being related to study treatment. There were no DLTs observed, and this Phase Ib study is completed.

4.2.5 Conclusion for dose regimen selection

Every 3 weeks dosing schedule of canakinumab is feasible based on its half-life of 26 days, and its ability to suppress CRP for at least 1 month as previously demonstrated in two single-dose phase II studies with dose ranges of 0.03 to 10 mg/kg i.v. and 25 to 300 mg s.c. Study [CACZ885A2213] in diabetes and Study [CACZ885H2251] in gouty arthritis respectively. More importantly, given the evidence of the efficacy profile from the CANTOS study in which canakinumab shows no plateau effect in lung cancer risk reduction at 300 mg s.c. quarterly (Q12W), and the comprehensive and well-established safety profile of canakinumab across a wide range of doses and dosing intervals studied in interventional trials, a 200 mg s.c Q3W dosing schedule for canakinumab, which has an approximately equivalent total dose amount and similar predicted PK range as 300 mg s.c. Q4W (a regimen already used in certain approved indications), is selected for the NSCLC development program to ensure a positive benefit/risk ratio. The protocol includes appropriate safety assessment to monitor and manage these risks (Section 6.5 for further details). The full dose of pembrolizumab (200 mg Q3W) and pemetrexed (500 mg/m^2) is expected to be administered as no additive toxicity is anticipated from this triple combination.

If canakinumab dosed at 200 mg s.c. Q3W is deemed intolerable in this triple combination based on data from the safety run-in part, an alternative canakinumab schedule will be implemented with increasing dosing interval of canakinumab, i.e. 200 mg s.c. Q6W

(Section 6.5.1.1). Based on population PK simulation, 200 mg s.c. Q6W is predicted to generate steady-state PK parameters (i.e. minimum concentration (Cmin), Cmax, average concentration (Cavg) that are lower than those from 200 mg s.c. Q3W, but still higher than those from the CANTOS top dose of 300 mg s.c. Q12W to ensure sufficient clinical benefit given the exposure-dependent risk reductions in lung cancer and lung cancer mortality observed from CANTOS.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Two phase III studies KEYNOTE 189 and KEYNOTE 407 (Section 1.1) establishes the combination of pembrolizumab in combination with platinum-based doublet chemotherapy in the first-line treatment for NSCLC. Despite these advances, the PFS and OS remain short and there is a need to improve efficacy. IL-1β inhibition is a new mechanism of action that is expected to bring benefit to NSCLC patients as suggested by the CANTOS study outcome. Additionally, the demonstrated correlation between the IL-1β pathway, CRP levels and PD-L1 expression provides a rationale for combining PD-1 inhibitors with an IL-1β pathway antagonist (Akamine et al 2018, Guo et al 2017). In studies that included 33567 and 10408 cancer-free individuals, elevated baseline levels of hs-CRP were demonstrated to be associated with increased mortality from lung cancer (Ko et al 2012, Allin et al 2009). Based on the immunomodulatory properties of IL-1β inhibition, it is expected that the maintenance treatment combination of canakinumab and pembrolizumab will lead to better outcomes than pembrolizumab alone as maintenance following induction treatment with platinum-based doublet chemotherapy plus pembrolizumab. Additionally, recent pooled data from the atezolizumab in second and later treatment line NSCLC studies demonstrate that decreases in CRP correlate with higher RECIST 1.1 responses and prolonged PFS and OS in the atezolizumab-treated arm, reinforcing the importance of inflammation as a target in cancer treatment (Patil et al 2018).

Rationale for choice of chemotherapies tested in safety run-in part (part 1)

The overlapping toxicities between canakinumab and the chemotherapies (carboplatin/cisplatin + pemetrexed; paclitaxel/nab-paclitaxel + carboplatin) include myelosuppression, febrile neutropenia and the increased risk of serious infections. Frequency of neutropenia, febrile neutropenia, thrombocytopenia and sepsis from selected Phase III studies of pemetrexed, nab-paclitaxel and paclitaxel in advanced NSCLC are summarized in Table 4-2 . For further details for the rationale for the choice of chemotherapy tested in safety run-in part refer to Section 1.1.1.1 .

Since the hematological events and febrile neutropenia events are similar for nab-paclitaxel and paclitaxel regardless of the NSCLC histology, paclitaxel will be used in the safety run-in to evaluate the safety of canakinumab added to pembrolizumab + paclitaxel + carboplatin. Results from the paclitaxel combination will be applied to nab-paclitaxel combination.

Based on the low number of all grade neutropenia and sepsis events observed with canakinumab monotherapy treatment in CANTOS study, it is expected that the addition of canakinumab to the combination of pembrolizumab and chemotherapy may only slightly increase the frequency of hematologic and infection related adverse events.

Table 4-2 Summary of key hematological and infection adverse events for different treatment combinations for NSCLC

Combination	N	Neutropenia % CTC grade 3/4	Febrile Neutropenia %	Thrombopenia % CTC grade 3/4	Infection % CTC grade 3/4	Reference
Pembrolizumab + Pemetrexed + platinum vs. Placebo + Pemetrexed + platinum	607 Safety Data set	15.8 vs. 11.9*	Not Reported (febrile neutropenia was the only adverse event of grade 3 or higher that was more frequent in pembrolizumab-combination group*)	7.9 vs. 6.9	Not reported	Gandhi et al 2018
Paclitaxel + cisplatin vs. Paclitaxel + carboplatin	608 Safety Data set	51 vs. 54	4 vs. 6	2 vs. 8	5 vs. 5	Rosell et al 2002
Paclitaxel + carboplatin vs. nab-paclitaxel + carboplatin	1038 Safety Data set	58 vs. 47	<2 vs. <2	9 vs. 18	Not reported	Socinski et al 2012
CANTOS Canakinumab 300 mg, 150 mg, 50 mg – Total vs. placebo	10061 CANTOS study, **events of all grades**	All Grades: 2.0,1.4,1.1-1.5 vs. 0.9	Not Reported	All Grades 2.7, 2.0, 2.0-2.2 vs. 1.6	Events of sepsis: 2.2, 2.1, 1.8-2.0 vs. 1.3	CANTOS study CSR
* Gandhi et al 2018 pembrolizumab included grade 5 in neutropenia data set.						

4.4 Purpose and timing of interim analyses/design adaptations

The statistical basis for claim of efficacy in favor of the canakinumab arm is based on either statistical significance for PFS or statistical significance for OS as detailed in Section 12.4.2.

The timing of the final PFS analysis and interim OS analyses are detailed in Section 12.4.2 and Section 12.7 .

4.5 Risks and benefits

The double-blind, randomized, placebo-controlled part of this Phase III study is preceded by a safety run-in, to define the dose of canakinumab to be used as RP3D. Appropriate eligibility criteria, specific dose-limiting toxicity definitions, and specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided in Section 6 .

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, and the periodic review of safety data by an independent data monitoring committee (DMC).

Cancer subjects receiving chemotherapy are at an increased risk of infection due to myelosuppression. Canakinumab treatment also predisposes subjects to an increased risk of infection. Nadir complete blood counts with differentials will be followed carefully during induction chemotherapy and urinalyses will be routinely performed on study visits to allow early diagnosis of potential urinary tract infections. Subjects are informed by their signed informed consent to notify their physician and seek medical attention immediately if they experience a fever (>38.0°C) or any signs/symptoms of infection. Refer to the [Investigator's Brochure].

Women of child-bearing potential and sexually active males must be informed that taking the study treatment 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 requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Imaging studies (computed tomography (CT), magnetic resonance or X-rays) will be used in this study to assess response of tumors to administered treatments. The frequency is consistent with the standard of care assessments every 6 weeks of chemotherapy. Tumor assessments required by the trial allow for magnetic resonance imaging (MRI) and CT; the ability to use of MRI instead of CT for the brain and abdomen decreases the radiation exposure. Only in the chest is CT preferable to MRI. Contrast enhancement is a standard tool to evaluate potential metastatic lesions; subjects with contrast allergy are exempted from its use. The ordering physician should assure that subjects are well hydrated and precautions taken to avoid renal injury due to contrast agents.

Advanced/metastatic NSCLC is an incurable disease, which has a median life expectancy of less than 20 months. Given that canakinumab or canakinumab matching-placebo is being added the most current standard of care for this disease, pembrolizumab in combination with platinum-based doublet chemotherapy, with subject safety overseen by a DMC, the risk benefit ratio favors canakinumab.

4.6 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e. pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure subject safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency will be discussed with Novartis by Investigator /Site prior to implementation of mitigation procedures and permitted/approved by local or regional Health Authorities and Ethics Committees as appropriate.

4.7 End of study definition

Study completion is defined when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator (e.g., each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them in the scope of the trial). The study will end when all participants discontinue the study treatment and complete their safety follow up, die, withdraw consent, or are lost to follow up, whichever comes first.

5 Population

The study population will include adult subjects to be treated in the first-line setting, advanced or metastatic non-small cell lung cancer (NSCLC), without EGFR or ALK alteration.

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

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained prior to any screening procedures
2. Adult male/female ≥ 18 years of age at the time of informed consent
3. Histologically confirmed locally advanced stage IIIB/IIIC (and is not eligible for definitive chemo-radiation curative therapy) or stage IV (metastatic) NSCLC for treatment in the first-line setting
    - Subjects who received previous neo-adjuvant or adjuvant systemic therapy (other than immunotherapies) will be eligible if neo-adjuvant or adjuvant therapy was completed at least 12 months prior to the development of metastatic disease. Last dose of neo-adjuvant or adjuvant therapy must be more than 12 months prior to enrollment/randomization
4. Subject is a suitable candidate for platinum-doublet chemotherapy and pembrolizumab, and does not have any contraindication(s) to these drugs as per locally approved label.
5. Known PD-L1 status determined by a Novartis designated central laboratory.
    - A newly obtained tissue biopsy or an archival biopsy (block or slides) is required for PD-L1 determination (PD-L1 IHC 22C3 pharmDx assay), prior to study randomization.
    - Note: For the safety run-in part, known PD-L1 status is not required.
6. ECOG performance status (PS) of 0 or 1.
7. At least 1 measurable lesion by RECIST 1.1 in solid tumors criteria; a previously irradiated lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
8. Subject must have recovered from all toxicities related to prior systemic therapy to grade ≤ 1 (CTCAE v5.0). Exception to this criterion: patients with any grade of alopecia
9. Subjects must have adequate bone marrow organ function including the following laboratory values at the screening visit:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (without growth factor support)
    - Platelets ≥ 100 x 10^9/L (without growth factor support or transfusion)
    - Hemoglobin (Hgb) > 9 g/dL (4 weeks without transfusions or erythropoietin)
    - Creatinine clearance greater than 60 mL/min by calculation using Cockcroft-Gault formula
    - Total bilirubin (TBIL) ≤ 1.5 x ULN
    - Aspartate aminotransferase (AST) ≤ 3 x ULN
    - Alanine aminotransferase (ALT) ≤ 3 x ULN
    - Serum amylase ≤ 2 x ULN or pancreatic amylase ≤ 1.5 x ULN

- Serum lipase ≤ 1.5 x ULN

10. Subject is able to communicate with the investigator, and has the ability to comply with the requirements of the study procedures.

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study.

1. Previous immunotherapy (e.g. anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways).
2. Prior treatment with canakinumab or drugs of a similar mechanism of action (IL-1β inhibitor).
3. Subjects with epidermal growth factor receptor (EGFR) sensitizing mutations , and/or ALK rearrangement by locally approved laboratory testing (If local testing is not available, a Novartis designated central laboratory will perform EGFR and/or ALK testing).
   - Subjects with NSCLC of pure squamous cell histology can initiate treatment without molecular testing or result, however, subjects with pure squamous cell histology that are known to have EGFR/ALK sensitizing mutations are excluded.
   - Subjects with known BRAF V600 mutation or ROS-1 rearrangement will be excluded, if required by local guidelines
4. History of severe hypersensitivity reaction to monoclonal antibodies, platinum containing drugs, paclitaxel, nab-paclitaxel, pemetrexed or any known excipients of these drugs (i.e. Polysorbate-80-containing infusions, mannitol, histidine).
5. Known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
   - Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 2 weeks and, have no evidence of new or enlarging brain metastases and also are off steroids ≥ 2 weeks (unless receiving a dose equivalent to prednisone ≤5 mg) prior to dosing with study medication. Stable brain metastases by this definition should be established prior to the first dose of study medication.
   - Subjects with known untreated, asymptomatic brain metastases (i.e., no neurological symptoms, no requirements for corticosteroids, no or minimal surrounding edema, no lesion >1.0 cm and a maximum of 3 lesions) may participate but will require regular imaging of the brain as a site of disease.
6. Presence or history of a malignant disease, other than NSCLC, that has been diagnosed and/or required therapy within the past 3 years prior to randomization. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type
7. Active autoimmune disease that has required systemic treatment in the past 2 years prior to randomization (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Control of the disorder with replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc) is permitted.
8. Subject with suspected or proven immunocompromised state or infections, including:
   - Evidence of active or latent tuberculosis (TB) as determined by locally approved screening methods. If the results of the screening per local treatment guidelines or clinical practice require treatment, then the patient is not eligible.
   - Chronic or active hepatitis B or C

- Known history of testing positive for Human Immunodeficiency Virus (HIV) infections. For countries where HIV status is mandatory: testing positive for HIV during screening using a local test.
- Any other medical condition (such as active infection, treated or untreated), which in the opinion of the investigator places the patient at an unacceptable risk for participation in immunomodulatory therapy.
  - Note: Subjects with localized condition unlikely to lead to a systemic infection e.g. chronic nail fungal infection are eligible.
- Allogeneic bone marrow or solid organ transplant
- Treatment with any immune modulating agent in doses with systemic effects e.g.:
  - Prednisone > 20 mg (or equivalent) oral or intravenous daily for > 14 days;
  - Prednisone > 5 mg and ≤ 20 mg (or equivalent) daily for > 30 days;
  - Equivalent dose of methotrexate > 15 mg weekly
  - Subject receiving any biologic drugs targeting the immune system (for example, TNF blockers, anakinra, rituximab, abatacept, or tocilizumab).
  - Note: Daily glucocorticoid-replacement for conditions such as adrenal or pituitary insufficiency is allowed.
  - Note: Topical, inhaled, or local steroid use in doses that are not considered to cause systemic effects are permitted.
  - Note: Steroids for pre-medication related to chemotherapy as per local standard of care are permitted.

9. Subject has received live vaccination within 3 months prior to first dose of study drug.
10. Subject has had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to starting study drug or has not recovered from side effects of such procedure (≥ grade 2 AE related to such procedure). Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and subject can be enrolled in the study ≥ 1 week after the procedure.
11. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or subjects who have not recovered from radiotherapy-related toxicities (≥ grade 2 AE related to such procedure). For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.
12. Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as:
    - Unstable angina or myocardial infarction within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Clinical significant cardiac arrhythmias
    - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, unless controlled prior to screening.

13. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.
14. Subject has any other concurrent severe and/or uncontrolled medical condition that would, in the investigator's judgment, cause unacceptable safety risks, contraindicate subject participation in the clinical study, or compromise compliance with the protocol (e.g. chronic pancreatitis, uncontrolled diabetes mellitus).
15. Known active or recurrent hepatic disorder including cirrhosis.
16. Patient is concurrently using other anti-cancer therapy
17. Participation in a prior investigational study (drug or device) within 30 days prior to enrollment or randomization or within 5-half lives of the investigational product, whichever is longer, or those who are expected to receive any other investigational drug or device during the conduct of the study.
18. Pregnant or breast-feeding (lactating) women, or women who plan to become pregnant or breast-feed during the study, 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.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during the study and 6 months after study treatment discontinuation. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject . Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception)
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient.
    - Use of oral (estrogen and progesterone), injected or implanted combined 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 stabilized on the same pill for a minimum of 3 months before taking study treatment.

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or bilateral tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.
20. Sexually active males unless they use a condom during intercourse while taking chemotherapy drug(s) and for 6 months after stopping chemotherapy treatment, and should not father a child in this period or as per the local label. A condom is required to be used

also by vasectomized men in order to prevent delivery of the chemotherapy drug(s) via seminal fluid.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects

6 Treatment

6.1 Study treatment

In this study, the "study treatment" refers to the combination of study drugs: canakinumab/canakinumab matching placebo, pembrolizumab, carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and pemetrexed. The term "investigational drug" refers to the Novartis study drug, canakinumab (ACZ885).

For all non-investigational drugs (pembrolizumab, carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and pemetrexed), the locally approved label and local practice are to be followed.

The choice of the chemotherapy medications (as described in the following sections) will be determined by the investigator prior to enrollment/randomization. This choice will be made based on the histology of the patients (and depending on what part the study the subject is participating to) and as per local practice and cannot be changed afterward. Of note, the choice to treat non-squamous subjects with pemetrexed after the 4 induction cycles will be determined by the investigator according to locally approved label and local practice.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the appropriate eCRF page.

6.1.1 Investigational and control drugs

6.1.1.1 Dosing regimen for Part 1: Safety run-in part

In the safety run-in (Part 1), 3 study treatment regimens will be tested in 3 cohorts of subjects (cohort A, cohort B, and cohort C) as defined in Table 6-1 . Subjects with non-squamous histology can be enrolled either in cohort A, B, or C. The choice of the chemotherapy medications in cohort A and B (see also Figure 3-1) will be determined by the investigator prior to enrollment (as per local practice). Subjects with squamous histology must be enrolled in cohort C.

Please note that canakinumab dose level (-1), canakinumab Q6W, may be investigated after review of the data collected for the Q3W regimen (Section 6.5).

Table 6-1 Part 1 (safety run-in part) - Cohort A: Dose and treatment schedule (non-squamous subjects only)

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen
Canakinumab (ACZ885)	Solution for s.c. injection in prefilled syringe	150 mg/1 mL AND 50 mg/0.5 mL	200 mg	Q3W (or Q6W)

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen
Pembrolizumab[a]	Concentrate for solution for i.v. infusion in vial	100 mg/4 mL (25 mg/mL)	200 mg	Q3W
	Lyophilized powder for solution for infusion in vial	50 mg		
Carboplatin	Concentrate for solution for i.v. infusion in vial	As per local label and practices	AUC 5 mg/mL*min	
Pemetrexed[b]			500 mg/m^2	
[a] Either concentrate solution or lyophilized powder formulations of pembrolizumab can be used if approved by local country regulations . [b] Pemetrexed can be given as maintenance therapy for patients with non-squamous NSCLC after induction treatment per investigator discretion according to local approved label and local practice.				

Table 6-2 Part 1 (safety run-in part) - Cohort B: Dose and treatment schedule (non-squamous subjects only)

Study Treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen
Canakinumab (ACZ885)	Solution for s.c. injection in prefilled syringe	150 mg/1 mL AND 50 mg/0.5 mL	200 mg	Q3W (or Q6W)
Pembrolizumab[a]	Concentrate for solution for i.v. infusion in vial	100 mg/4 mL (25 mg/mL)	200 mg	Q3W
	Lyophilized powder for solution for infusion in vial	50 mg		
Cisplatin	Concentrate for solution for i.v. infusion in vial	As per local label and practices	75 mg/m^2	
Pemetrexed[b]			500 mg/m^2	
[a] Either concentrate solution or lyophilized powder formulations of pembrolizumab can be used if approved by local country regulations. [b] Pemetrexed can be given as maintenance therapy for patients with non-squamous NSCLC after induction treatment per investigator discretion according to local approved label and local practice.				

Table 6-3 Part 1 (safety run-in part) - Cohort C: Dose and treatment schedule (squamous or non-squamous subjects)

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen
Canakinumab (ACZ885)	Solution for s.c. injection in prefilled syringe	150 mg/1 mL AND 50 mg/0.5 mL	200 mg	Q3W (or Q6W)
Pembrolizumab[a]	Concentrate for solution for i.v. infusion in vial	100 mg/4 mL (25 mg/mL)	200 mg	Q3W

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen
	Lyophilized powder for solution for infusion in vial	50 mg		
Carboplatin	Concentrate for solution for i.v. infusion in vial	As per local label and practices	AUC 6 mg/mL*min	
Paclitaxel			200 mg/m^2	
Pemetrexed[b]	Concentrate for solution for i.v. infusion in vial	As per local label and practices	500 mg/m^2	
[a] Either concentrate solution or lyophilized powder formulations of pembrolizumab can be used if approved by local country regulations. [b] Pemetrexed can be given as maintenance therapy for patients with non-squamous NSCLC after induction treatment per investigator discretion according to local approved label and local practice.				

6.1.1.2 Dosing regimen for Part 2: double-blind, randomized, placebo-controlled part

In the double-blind, randomized, placebo-controlled part (Part 2), subjects will be randomized into 2 study treatment arms with canakinumab or canakinumab matching-placebo. The study treatment will be canakinumab/matching placebo in combination with pembrolizumab and platinum-based doublet chemotherapy (with or without pemetrexed). The platinum-based doublet chemotherapies (carboplatin plus paclitaxel/nab-paclitaxel vs. pemetrexed plus carboplatin/cisplatin) are dependent on the tumor histology of the subject (squamous vs. non-squamous) as defined in Table 6-4 . Note: subjects with adenosquamous histology can be treated as either squamous or non-squamous histology; see Section 6.3.2. The chemotherapy treatment selected must match the histology selected in the IRT system at time of randomization (squamous or non-squamous).

Table 6-4 Part 2 (double-blind, randomized, placebo-controlled part): Dose and treatment schedule

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen	Histology
Canakinumab (ACZ885)	Solution for s.c. injection in prefilled syringe	150 mg/1 mL AND 50 mg/0.5 mL	200 mg	Q3W or Q6W[b]	Squamous AND non-squamous
Canakinumab matching-placebo (ACZ885)		0 mg/1 mL AND 0 mg/0.5 mL	0 mg		
Pembrolizumab [a]	Concentrate for solution for i.v. infusion in vial	100 mg/4 mL (25 mg/mL)	200 mg	Q3W	
	Lyophilized powder for solution for infusion in vial	50 mg			

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen	Histology
Carboplatin OR cisplatin	Concentrate for solution for i.v. infusion in vial	As per local label and practices	AUC 5 mg/mL*min (carboplatin) OR 75 mg/m^2 (cisplatin)		Non-squamous
Pemetrexed			500 mg/m^2		
Carboplatin			AUC 6 mg/mL*min		Squamous
Paclitaxel OR nab-paclitaxel			200 mg/m^2 (paclitaxel) OR 100 mg/m^2 (nab-paclitaxel)		
[a] Either concentrate solution or lyophilized powder can be used per locally approved label and local practice; [b] Depending on RP3R (recommended phase 3 regimen) defined during safety run-in part (Part 1)					

6.1.1.3 Dosing regimen for the Open Label Extension phase

Subjects enrolled in the SRI part and subjects randomized to the canakinumab arm in the randomized part will transition into the OLE with their current treatment and dosing regimen.

Subjects randomized to the canakinumab matching-placebo arm in the randomized part will be allowed to cross over to canakinumab, per investigator and subject discretion, provided they fulfill crossover criteria (Section 6.1.3). Subjects who cross over to canakinumab are recommended to start canakinumab at 200mg s.c. Q3W dosing regimen.

6.1.1.4 Dosing regimen post implementation of protocol amendment 06

As of 05-Sep-2022, there are no more subjects on treatment taking pembrolizumab. All subjects enrolled in the SRI part have discontinued treatment. The trial was unblinded as of 25-Oct-2021 and subjects were allowed to continue treatment with pembrolizumab and pemetrexed plus canakinumab (as applicable) if the investigator considered this beneficial for the subject. As of 25-Aug-2023, there are 18 subjects on treatment, 5 of them taking canakinumab in combination with pemetrexed, 6 taking canakinumab alone, and 7 taking pemetrexed alone.

Table 6-5 Dose and treatment schedule post implementation of protocol amendment 05

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen	Histology
Canakinumab (ACZ885)	Solution for s.c. injection in prefilled syringe	150 mg/1 mL and 50 mg/0.5 mL	200 mg	Q3W (or Q6W)	Squamous and non-squamous
	Solution for s.c. injection in prefilled syringe	200 mg/1.33 mL			

Study treatment	Pharmaceutical Dosage Form and route of administration	Strength	Dose	Frequency and/or regimen	Histology
Pemetrexed	Concentrate for solution for i.v. infusion in vial	As per local label and practices	500 mg/m^2	Q3W	Non-squamous

Table 6-6 Investigational and study drug post implementation of protocol amendment 06

Treatment Title	Canakinumab (ACZ885)	Canakinumab (ACZ885)	Pemetrexed
Treatment Description	Canakinumab	Canakinumab	Pemetrexed
Type	biologic	biologic	chemotherapy
Dose Formulation	Solution for s.c. injection in prefilled syringe	Solution for s.c. injection in vial	As per local label and practices
Unit Dose Strength(s)	200 mg/1.33 mL	150 mg/1 mL	500 mg/m^2 Q3W
Dosage Level(s)	200 mg Q3W (or Q6W)	200 mg Q3W (or Q6W)	500 mg/m^2 Q3W
Route of Administration	Subcutaneous Injection	Subcutaneous Injection	i.v. infusion
Use	experimental	experimental	additional study drug
IMP	Yes	Yes	No
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Locally sourced
Packaging and Labeling	Study treatment will be provided as solution for s.c. injection in pre-filled syringe. Each pre-filled syringe will be labeled as required per country requirement.	Study treatment will be provided as solution for s.c. injection in vial. Each vial will be labeled as required per country requirement.	As per local label and practices

6.1.1.5 Supply and administration of study treatment

Post trial unblinding on 25-Oct-2021, canakinumab-matching placebo was no longer supplied nor administered.

Supply of study treatment

Canakinumab and canakinumab matching-placebo will be supplied by Novartis or its designee in the pharmaceutical form of solution for s.c. injection as ready-to-use pre-filled syringes.

Post implementation of protocol amendment 05, once 150 mg/1 mL and 50 mg/0.5 mL solution for s.c. injection as pre-filled syringes are no longer available, canakinumab will be supplied in the pharmaceutical form of 200 mg/1.33 mL solution for s.c injection as ready-to-use pre-filled syringes (Table 6-5).

Post implementation of protocol amendment 06, once 200 mg/1.33 mL solution for s.c. injection as pre-filled syringes is no longer available, canakinumab will be supplied in the pharmaceutical

form of 150 mg/1 mL solution for s.c. injection in vial (Table 6-6). The dose of canakinumab to be given in this current study part 2 (double-blind, randomized, placebo-controlled part) is unchanged (200 mg s.c).

CCI [redacted] A bioequivalence study, CACZ885A2104, demonstrated the bioequivalence of solution for injection in a pre-filled syringe and lyophilized form of canakinumab. Additionally, population PK analysis of PK data from study CACZ885N2301 showed no effect of formulation between lyophilized form of canakinumab and solution for s.c injection in vial on the PK of canakinumab. CCI [redacted]

The 150 mg/1 mL solution for injection in vial, 150 mg/1 mL solution for injection in prefilled syringe and 200mg/1.33 mL solution for injection in prefilled syringe have the same formulation.

An analytical comparability assessment between the 150 mg/1 mL solution for injection in vial, 150 mg/1 mL solution for injection in the prefilled syringe, and 200 mg/1.33 mL solution for injection in prefilled syringe was performed which demonstrated they are comparable from a quality perspective.

The drug substance is manufactured with the same process and at the same manufacturing site that is approved for the marketed product Ilaris 150 mg/1 mL solution for injection in vial.

Pembrolizumab and the chemotherapies (carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and pemetrexed) will be provided locally by the study site, subsidiary or designee as commercially available or centrally by Novartis, in each participating country according to local practices and local regulations.

For dose and treatment schedule refer to Figure 6-1 and Figure 6-2, and for allowable visit windows refer to Table 8-1.

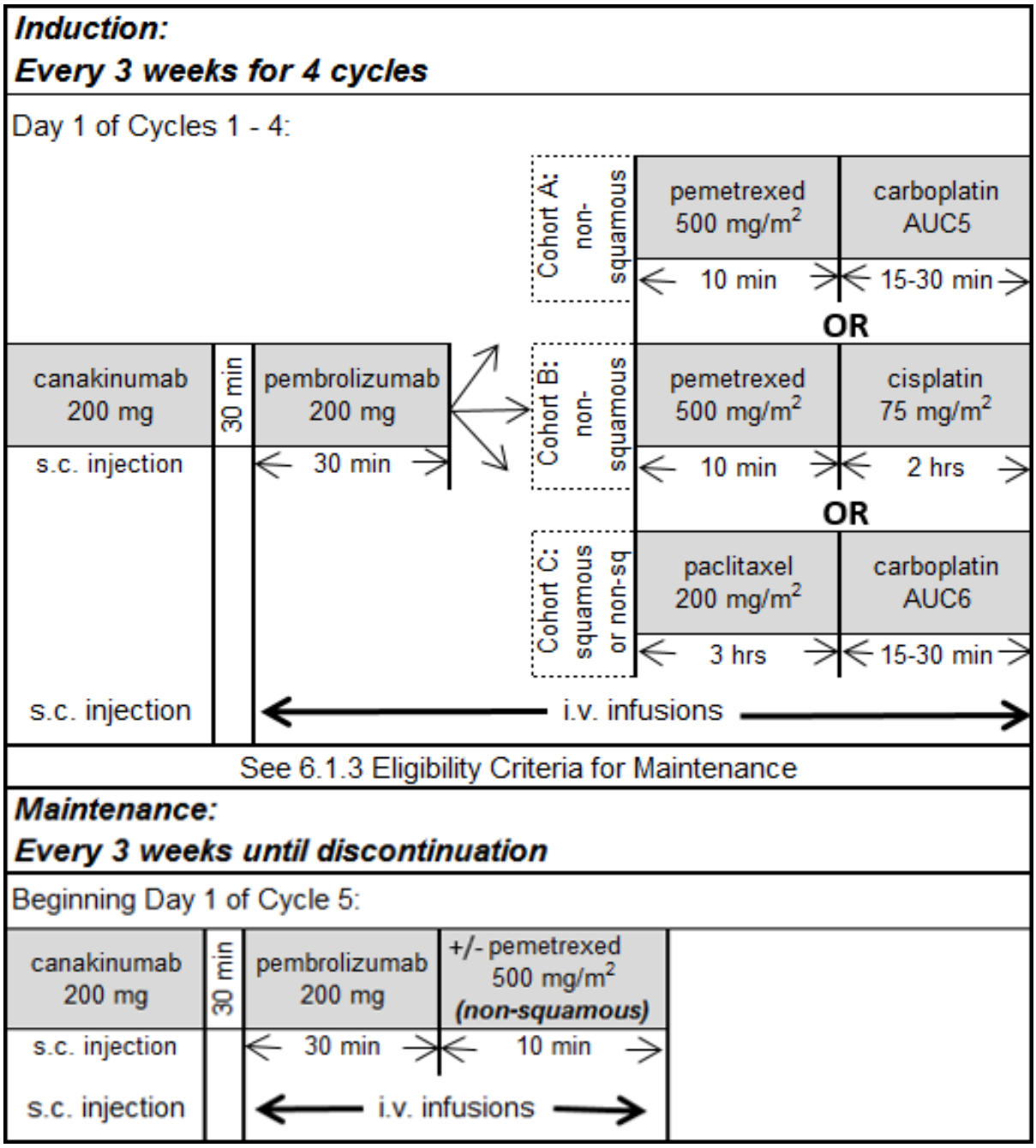
Administration of study treatment

Canakinumab or canakinumab matching-placebo will be administered by study site personnel via s.c. injections once every 3 weeks or 6 weeks as determined in part 1 (safety run-in part).

The administration and infusion durations of the study drugs (pembrolizumab, platinum-based doublet chemotherapy, and pemetrexed) should follow the locally approved label and local practice.

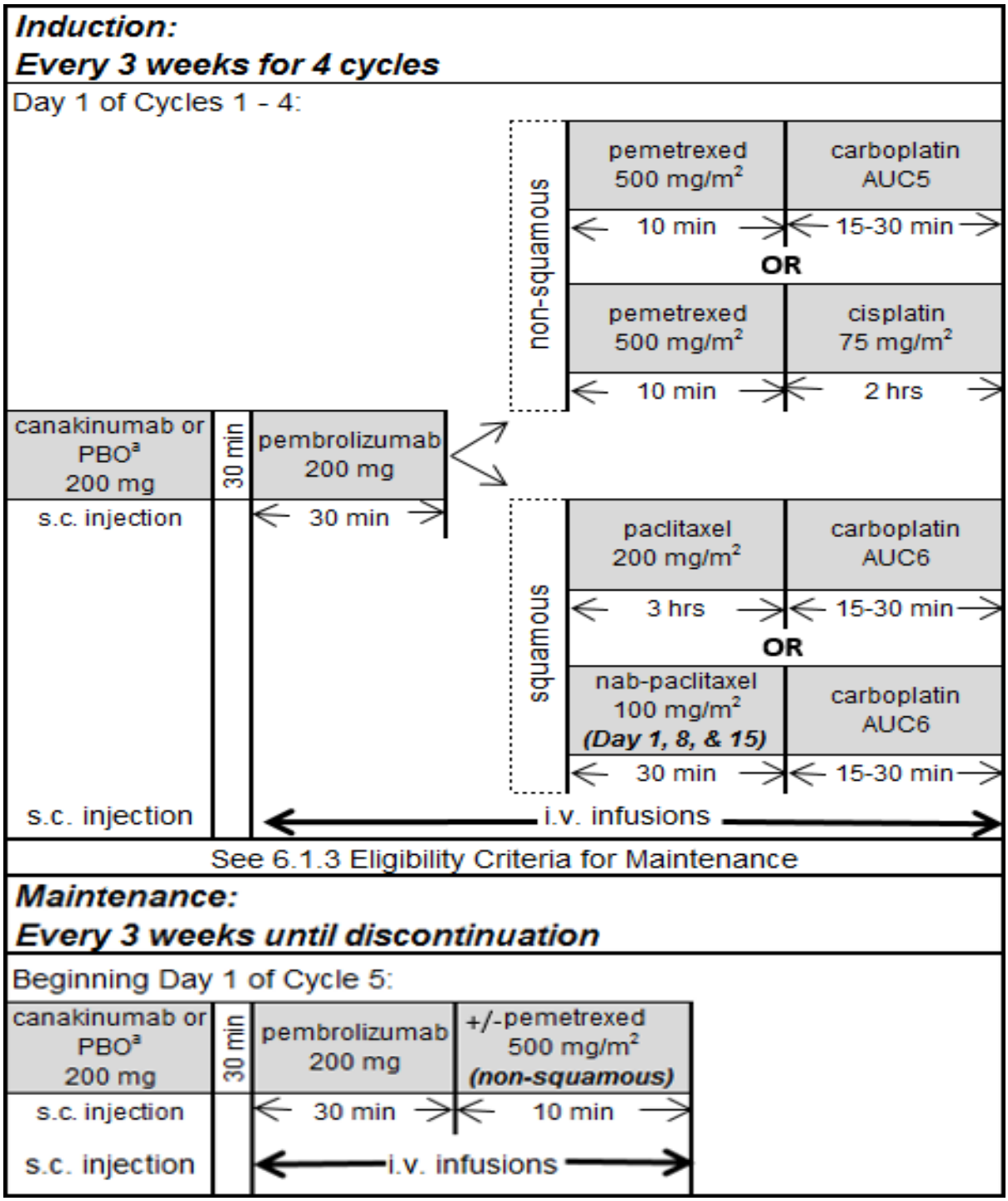
All study drugs should be administered sequentially, on the same day as reported in Figure 6-1 and Figure 6-2 .

Figure 6-1 Safety run-in part: dose and treatment schedule



Note: The infusion times reported for chemotherapies, and pembrolizumab (30 min: -5 min/+10 min), are suggestions only. The locally approved labels and local practice are to be followed.

Figure 6-2 Double-blind, randomized, placebo-controlled part including optional crossover in the OLE phase and post implementation of protocol amendment 05: dose and treatment schedule



[a]RP3R defined during safety run-in. Placebo (PBO) is not applicable during the OLE phase. Post trial unblinding on 25-Oct-2021, canakinumab-matching placebo was no longer supplied nor administered. Note: The infusion times reported for chemotherapies, and pembrolizumab (30 min: -5 min/+10 min), are suggestions only. The locally approved labels and local practice are to be followed.

6.1.2 Additional study treatments

All subjects receiving pemetrexed as part of study treatment (non-squamous NSCLC histology only) should be premedicated with folic acid, vitamin $_{B12}$ and glucocorticoids as required per locally approved label and local practice.

Alternative premedication dosing or schedule may be administered as per locally approved label and local practice.

6.1.3 Guidelines for continuation of treatment

Guidelines for management of toxicities and doses modifications instructions

Please refer to Section 6.5.3 .

Criteria for continuation of study treatment from induction to maintenance

All subjects are expected to receive 4 cycles of induction treatment: canakinumab (or canakinumab matching-placebo) in combination with pembrolizumab plus platinum-based doublet chemotherapy. After induction, all subjects are expected to continue in maintenance with canakinumab/matching placebo in combination with pembrolizumab.

Only subjects with non-squamous histology who achieve stable disease (SD) or better radiological response after induction treatment will be eligible to continue pemetrexed during maintenance.

However, treatment beyond RECIST 1.1 progressive disease is allowed, please refer to Section 6.1.4.1 for details.

Criteria for crossover from canakinumab matching-placebo arm to canakinumab in the OLE phase

During the OLE phase, subjects randomized to the canakinumab matching placebo arm will be allowed to cross over to canakinumab, if the investigator determines this is in the subject's best interest and per subject discretion (Section 3). Crossover is optional.

A subject is eligible to cross over if the following criteria are met:

1. No evidence of active infection – subjects with active infections must wait until the infection is resolved and antibiotic therapy (if initiated) is completed prior to crossover. Note: subjects with localized condition unlikely to lead to a systemic infection, e.g. chronic nail fungal infection are eligible.
2. Subjects with neutropenia and/or thrombocytopenia must wait until these are resolved to ≤ grade 2
3. No suspected or proven immunocompromised state, as per exclusion criterion 8
4. AST/ALT < 3.0 x ULN
5. bilirubin < 3.0 x ULN
6. pancreatitis ≤ grade 2

Subjects who do not fulfill these requirements and subjects who do not cross over to canakinumab within 12 weeks from time of investigational site unblinding, will transition into

the OLE with their current treatment only (i.e. pembrolizumab and maintenance chemotherapy, where applicable, and not canakinumab matching placebo).

6.1.4 Treatment duration

Subjects will continue to receive study treatment until RECIST 1.1 disease progression is radiologically documented by investigator assessment (exceptions are described in Section 6.1.4.1), unacceptable toxicity that precludes further treatment, treatment is discontinued at the discretion of the investigator, subject withdrawal of consent, pregnancy, lost to follow-up, or death (Section 9.1.1).

If pembrolizumab and all other study chemotherapy drugs are permanently discontinued because of unacceptable toxicities, the investigator can continue canakinumab/matching-placebo alone until RECIST 1.1 disease progression as per investigator, as long as:

- There is no radiological evidence of disease progression by RECIST 1.1, **and**
- The subject is continuing to benefit from investigational drug treatment as assessed by the investigator, **and**
- The subject is tolerating the treatment and clearly understands the risks associated with continuing treatment with canakinumab/matching-placebo, **and**
- Separate informed consent for canakinumab/matching-placebo alone until disease progression per RECIST 1.1 is provided by the subject.

For subjects randomized in part 2, no cross-over treatment from canakinumab matching-placebo treatment arm to canakinumab treatment arm will be allowed. However, if the OLE phase is initiated, subjects randomized to the canakinumab matching-placebo arm will be allowed to cross over to canakinumab if the investigator determines this is in the subject's best interest and per subject discretion, provided they fulfill crossover criteria. Crossover is optional.

6.1.4.1 Treatment beyond disease progression

Subjects who derive clinical benefit are permitted to continue study treatment beyond initial RECIST 1.1 disease progression as per investigator provided they meet all of the following criteria:

- Absence of confirmed PD by iRECIST (iCPD)
- Continuation of study treatment beyond initial RECIST 1.1 disease progression will not delay an imminent intervention to prevent serious complications of disease progression
- Subject performance status is stable
- Subject exhibits adequate tolerance to study treatment as defined by no grade 3 or 4 toxicities within the past 21 days on current therapy
- Separate informed consent for study treatment beyond disease progression per RECIST 1.1 is provided by the subject

If the above criteria are met, subjects are permitted to continue study treatment until immune confirmed disease progression (iCPD) per iRECIST as per investigator. Pembrolizumab treatment duration is a maximum of 35 administrations.

Canakinumab/matching placebo as single agent after RECIST 1.1 PD is not allowed.

If pembrolizumab is discontinued before disease progression per RECIST 1.1, treatment with canakinumab/matching placebo with chemotherapy (during induction or maintenance) is not allowed beyond RECIST 1.1 PD.

Study treatment beyond iRECIST confirmed disease progression (iCPD) may be allowed if the investigator determines it is in the best interest of the subject. In such cases, approval by a Novartis study physician is required.

All study procedures have to be followed as outlined in Section 8. Eligibility for the subject continuing study treatment beyond RECIST 1.1 PD will be documented in the eCRF.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In general, the use of any concomitant medications/non-drug therapies deemed necessary for the care of the subject (e.g. G-CSF, anti-emetics, anti-diarrhea) is permitted except when specifically prohibited (Section 6.2.2). For pembrolizumab and study chemotherapy drugs, please refer to the locally approved label.

The investigator should instruct the subject to notify the study site about any new medications and/or non-drug therapies/procedures he/she takes after signing the informed consent. All medications including herbal/natural medications and significant non-drug therapies/procedures (including surgeries, physical therapy and blood transfusions) taken within 28 days of screening and administered after the subject has signed informed consent must be listed on the appropriate eCRF pages.

Subjects taking concomitant medication chronically should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. The days of PK blood sampling should be representative of the other study days with regard to the use of the chronically administered concomitant medications. However, if a concomitant medication is used intermittently during the study, this medication should be avoided on the days of PK sampling, if medically feasible (Section 6.2.2).

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate eCRF page.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medications. If in doubt, the investigator should contact the Novartis medical monitor before enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, contact Novartis to determine if the subject should continue participation in the study.

Note: For Drug-Drug interaction (DDI) potential, please refer to Section 1.1.3 for DDI potential between canakinumab and combination partners.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

6.2.1.1.1 Permitted radiotherapy

Limited-field palliative radiation for bone pain is permitted.

Radiotherapy should not be delivered to a target lesion and it should not encompass more than 25% of irradiated bone marrow (Section 16.1). If palliative radiotherapy is initiated after the start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be ruled out. No dose modification of study treatment is needed during palliative radiotherapy.

After documented RECIST 1.1 PD, radiation therapy is allowed.

6.2.1.1.2 Permitted concomitant medications

Medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheal are allowed. Potential drug interactions between study drugs and concomitant medications should always be taken into consideration.

Except for paclitaxel/nab-paclitaxel, none of the chemotherapy agents (carboplatin, cisplatin, and pemetrexed) have major CYP enzyme involvement and are primarily eliminated by the kidney. The metabolism of paclitaxel/nab-paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering paclitaxel/nab-paclitaxel concomitantly with medicines known to inhibit or induce either CYP2C8 or CYP3A4. See Table 16-18 for drugs to be used with caution with paclitaxel/nab-paclitaxel while on study.

CYP450 expression may be normalized when potent cytokine inhibitory therapy, such as canakinumab, is introduced (see Section 1.1.3.1). This is clinically relevant for CYP450 substrates with a narrow therapeutic index. Caution should be exercised when administering these agents (see Table 16-19) concomitantly with canakinumab.

Given the potential DDI via cytokine modulation by canakinumab, subjects who are on warfarin or warfarin-like treatment with narrow therapeutic index, should have their international normalized ratio (INR) measured locally and warfarin or warfarin-like treatment dose adjusted accordingly within one month from starting study treatment. No DDI is expected between warfarin and the study chemotherapy drugs, as these drugs are eliminated by different elimination pathways (warfarin by CYP2C9, paclitaxel/nab-paclitaxel by CYP2C8 and CYP3A4, and other chemotherapy agents mainly via kidney) and are not an inhibitor/inducer of each other's metabolism.

6.2.2 Prohibited medication

6.2.2.1 Prohibited concomitant medications for canakinumab/matching placebo

Use of any treatments below are NOT allowed after the start of study treatment due to potential increase in immunosuppressant related concomitant conditions. They are prohibited for the duration of the study and for at least 130 days after discontinuation of canakinumab/matching-placebo.

Note: steroids are allowed at any dose/duration when necessary to treat immune-related adverse events (irAE). Investigators should closely monitor subjects for risk of infections.

- Any anti retro-virals and / or any biologic drugs targeting the immune system (e.g., TNFa blockers, anakinra, rituximab, abatacept, tocilizumab)

- Treatment with any immune modulating agent in doses with systemic effects e.g.:
  - Prednisone > 20 mg (or equivalent) oral or intravenous daily for > 14 days;
  - Prednisone > 5 mg and ≤ 20 mg (or equivalent) daily for > 30 days;
  - Equivalent dose of methotrexate > 15 mg weekly
- Topical, inhaled or local steroid use in doses that are not considered to cause systemic effects are permitted
- Steroids for pre-medication related to chemotherapy are permitted as per the locally approved label and local practice
- Live vaccines within 90 days of study treatment and after initiation of study treatment. Subjects must be discontinued from the trial if administered any live vaccine during the course of the study. *Note: Inactivated vaccines are allowed.*

The following treatments are NOT allowed after the start of study treatment and until the end of study treatment:

- Any additional investigational drugs, devices, chemotherapy, or any antineoplastic therapies that may be active against cancer.

6.2.2.2 Prohibited concomitant medications for pemetrexed

Subjects taking Non Steroidal Anti-Inflammatory Drugs (NSAIDs) or salicylates will not take the NSAIDs or salicylates (other than an aspirin dose ≤1.3 grams per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Subjects taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDs or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

6.3 Subject numbering, treatment assignment, randomization

The enrollment (safety run-in part) and randomization (randomized part) of the study has been completed. The trial was unblinded on 25-Oct-2021. The below Section 6.3.1 Subject numbering and Section 6.3.2 Treatment assignment, randomization are no longer applicable.

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first entered into screening and is retained as the primary identifier for the subject 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 subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the ICF, the subject is assigned the next sequential Subject No. available.

The investigator or designated staff will contact the Interactive Response Technology (IRT) and provide the requested identifying information to register the subject. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed. If the subject fails to be enrolled (safety run-in) or randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF page.

6.3.2 Treatment assignment, randomization

Prior to dosing, for all subjects who fulfill all inclusion/exclusion criteria, the investigator or his/her delegate will log on to the IRT system and confirm that the subject fulfills all the inclusion/exclusion criteria by completing the key eligibility criteria checklist embedded in the system. **Note: Cycle 1 Day 1 visit and dosing should occur no later than 3 days after IRT registration.**

The choice of the chemotherapy medications (Figure 3-1 and Figure 3-2) will be determined by the investigator prior to enrollment/randomization based on histology of the patient and as per local practice.

In the safety run-in part (part 1), no randomization will be performed. The assignment of a subject to a particular cohort will be coordinated by the investigator based on his/her choice of the chemotherapy medication.

In the double-blind, randomized, placebo-controlled part (part 2), subjects will be randomized in a 1:1 ratio to one of the 2 treatments arms (Section 4 and Section 6.1). The IRT system will generate a randomization number to the subject and provide a unique medication (kit) number for dispensation to the subject. The randomization number will not be communicated to the investigator or his/her delegate.

Randomization will be stratified based on PD-L1 status (Tumor Proportion Score (TPS) <1% vs. ≥1%), geographic region (East Asia **vs**. North America + Western Europe **vs**. Rest of the World), and histology (squamous vs. non-squamous). PD-L1 unevaluable subjects will be included with the TPS <1% group. Random permuted blocks scheme will be used for this study. Subjects with adenosquamous histology should be stratified as squamous or non-squamous based on the predominant histology or the histology chosen by the treating physician for determining treatment, if medically justified.

A separate medication randomization list will be produced by the IRT provider under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of subject numbers to medication packs containing the investigational drug.

Subject transition to OLE and crossover to canakinumab, if applicable, will be performed on the IRT system.

6.4 Treatment blinding

Part 1: Safety run-in part

Not applicable.

Part 2: Double-blind, randomized, placebo-controlled part

Only the investigational drug (canakinumab) will be blinded in this study.

At the time of the final PFS analysis, both PFS and 1st IA for OS will be performed by an independent statistician and reviewed by a data monitoring committee (DMC). Unblinded results from the final PFS analysis and IA for OS will not be communicated to the Sponsor's

clinical team or to any party involved in the study conduct (apart from the independent statistician and DMC members) until the DMC has determined that either:(i) final PFS or interim OS analyses has crossed the pre-specified boundary for efficacy or (ii) the study needs to be terminated due to any cause including safety reasons. If the final PFS and 1st IA for OS are not statistically significant, the 2nd IA for OS will also be done by an independent statistician. If the final PFS analysis is statistically significant, the sponsor's clinical team will be unblinded and will perform the second OS interim and/or final OS analyses. Subjects, investigator, site personnel, persons performing the assessments, will remain blinded to the identity of the treatment from the time of randomization until OS results are statistically significant at one of the interim or final analyses.

If OS reaches statistical significance at one of the interim or final analyses, all subjects on treatment or in safety/efficacy follow up will transition to the OLE phase following unblinding of investigational sites to treatment allocation. If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, OLE will be initiated after final OS analysis, following unblinding of investigational sites (Section 3). To limit the impact of unblinding on the scientific validity of the study results, individual subject unblinding is prohibited. Unblinding will only be permitted in the case of subject emergencies (Section 6.6.2), for regulatory reporting purposes. Unblinding is also permitted under exceptional circumstances if treatment assignment is critical to determine the optimal subsequent treatment for the subject and only if post-progression therapy with an IL-1ß inhibitor is being considered. In case of unblinding for determination of subsequent treatment, approval by a Novartis study physician is required.

Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the following exceptions: independent biostatistician and programmer who will perform Data Monitoring Committee (DMC) analysis, PK bioanalyst, modeler and modeling programmer. The study bioanalyst will receive a copy of the randomization schedule to facilitate analysis of the samples. The independent biostatistician and programmer and bioanalyst will keep treatment allocation information confidential until clinical database lock.

The trial was unblinded on 25-Oct-2021.

6.5 Dose escalation and dose modification

6.5.1 Dose confirmation guidelines

6.5.1.1 Starting dose

The starting dose of canakinumab is 200 mg s.c. Q3W for the safety run-in part (Section 6.1.1.1).

The recommended phase 3 dose regimen (RP3R) from the safety run-in part will be the starting dose for the part 2 (double-blind, randomized, placebo-controlled part) .

6.5.1.2 Guidelines for safety and tolerability decisions and determination of recommended Phase 3 dose Regimen (RP3R)

The primary objective is to establish the recommended Phase 3 dose regimen (RP3R) of canakinumab and pembrolizumab in combination with: pemetrexed and carboplatin in cohort

A (non-squamous subjects); pemetrexed and cisplatin in cohort B (non-squamous subjects), and paclitaxel and carboplatin in cohort C (squamous or non-squamous subjects). The primary variable is the incidence of dose limiting toxicities (DLTs) in the first 42 days of study treatment. Determination of the RP3R of canakinumab will be based upon the estimation of the probability of DLT for the first 42 days for subjects in the dose-determining set.

For the purposes of dose de-escalation decisions, **each cohort** will consist of approximately 9 enrolled subjects who will be treated at the specified dose level in order to have at least 6 evaluable subjects for the dose decision. The first dose level will be full dose of canakinumab and full dose of other components with possibility to de-intensify the administration of canakinumab only. Additional dose levels for dose de-escalation in subsequent cohorts will include provisional dose levels of canakinumab given less frequently, e.g. every 6 weeks (Q6W) instead of every 3 weeks (Q3W) with dose of other components maintained at the starting full dose.

Dose de-escalation decisions and RP3R decision 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 v5.0 Grade ≥ 2 toxicity data during first 42 days of treatment, and Pharmacokinetics (PK) data from the evaluable subjects. Dosing regimen decisions are guided by the escalation with overdose control (EWOC) principle (Rogatko et al 2007). The recommended canakinumab dose regimen for the next cohort of subjects will be guided by the Bayesian logistic regression model (BLRM) with EWOC principle (Section 16.3).

The adaptive Bayesian methodology provides an estimate of all dose levels in each cohort: canakinumab in combination with pembrolizumab, pemetrexed and carboplatin; canakinumab in combination with pembrolizumab, pemetrexed and cisplatin; or canakinumab in combination with pembrolizumab, paclitaxel and carboplatin, and incorporates all DLT information at all dose levels for this estimation.

If the first 2 subjects in a cohort experience a DLT, further enrollment to that cohort will stop and the BLRM will be updated with this new information. Re-evaluation of the available safety and PK data will occur. By incorporating information gained at the preceding dose levels, additional subjects may be enrolled at this dose level or a lower dose level as agreed by Investigators who enrolled subjects and Novartis personnel and if the BLRM predicts that the risk that this lower dose exceeds the toxicity remains below 25% (EWOC). Re-escalation may then occur if data in subsequent cohorts supports it (EWOC criteria are satisfied) and Investigators who enrolled subject and Novartis personnel agree.

Evaluable subjects will be defined as below:

- Have received full dose of pembrolizumab for at least 2 cycles and at least 75% of the planned dose of the 2 cycles of chemotherapy, **and**
- Have received at least 2 doses of canakinumab (for Q3W dosing regimen cohort) or at least 1 dose of canakinumab (for Q6W dosing regimen cohort in case the canakinumab dose is de-escalated to Q6W) , **and**
- Have been followed for the first 42 days (2 cycles) for adverse events starting Cycle 1 Day 1.

The RP3R is identified when the following conditions are met **in each cohort**:

- At least 6 evaluable subjects have been treated at this dose and observed for 42 days **and**

- This dose satisfies EWOC criteria **and**
- The selected dose regimen is recommended either per the model or by review of all clinical data by Dose Level Review Team (DLRT) in a dose decision meeting.

6.5.1.3 Provisional dose levels

Table 6-7 Provisional dose levels

Dose level (DL)	Canakinumab (s.c. injection)	Pembrolizumab (i.v. infusion)	Chemotherapy drugs (i.v. infusion)
DL1	200 mg Q3W	200 mg Q3W	pemetrexed 500 mg/m^2 **plus** carboplatin AUC 5 **OR** pemetrexed 500 mg/m^2 **plus** cisplatin 75 mg/m^2 **OR** paclitaxel 200 mg/m^2 **plus** carboplatin AUC 6
DL-1	200 mg Q6W	No change, same as above	No change, same as above

6.5.1.4 Implementation of dose regimen decisions

To implement dose regimen decisions, the available toxicity information (including adverse events and laboratory abnormalities that are not DLTs), the recommendations from the BLRM, and the available PK/PD (IL-1β) information will all be evaluated by the investigators who enrolled subjects and Novartis study personnel (including the study physician and statistician) during a dose decision meeting. Drug administration at the next lower dose level (canakinumab DL-1) may not be administered if the investigator receives written confirmation from Novartis indicating the results of the previous dose level were evaluated and that it is the recommended regimen.

Novartis will communicate the agreed dose decision in writing to the Dose Level Review Team (DLRT), data monitoring committee (DMC), steering committee (SC), and all participating investigators. Additional communication in a form of teleconference, webcast, or investigator meeting may be implemented if needed.

6.5.1.5 Implementation of dose escalation decisions

Not applicable

6.5.1.6 Intra-Subject dose escalation

Intra-subject dose escalation is not permitted at any time.

6.5.2 Definitions of dose limiting toxicities (DLTs)

Dose-limiting toxicities will be collected and used in the safety run-in part of the study (Part 1). A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 42 days of treatment with canakinumab and

pembrolizumab in combination with additional protocol specified chemotherapy and meets any of the criteria included in Table 6-8. The National Cancer Institute Common Terminology Criteria for Adverse events (NCI CTCAE v5.0) will be used for all grading. In addition to DLTs, the decision about the recommended Phase 3 regimen (RP3R) will be based on a synthesis of all relevant data available including all CTCAE v5.0 Grade ≥ 2 and PK data during the first 42 days of combination treatment from evaluable subjects. For the purpose of dose de-escalation decisions, DLTs will be considered and included in the BLRM.

The investigator must notify the sponsor immediately of any DLT.

Table 6-8 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA (NCI CTCAE v5.0 will be used for grading)
Hematological	• Grade 4 neutropenia (for >7 consecutive days). For paclitaxel combinations: for > 14 days* • Grade 4 febrile neutropenia • Grade 4 anemia • Grade 4 thrombocytopenia (<25,000/mm^3) any duration. For paclitaxel combinations: >7 days or associated with clinically significant bleeding (i.e. life threatening and invasive intervention indicated) # • Grade 3 thrombocytopenia with clinically significant bleeding (i.e. life threatening and invasive intervention indicated) regardless of duration or requirement for transfusion
Severe infection	• Drug-related grade 4
Hepato-biliary	• Grade 4 bilirubin elevation • For subjects with normal baseline AST and ALT values: AST or ALT > 8.0 × ULN • For subjects with normal baseline AST and ALT and normal baseline bilirubin value: AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN without evidence of cholestasis • For subjects with abnormal baseline AST or ALT or abnormal baseline bilirubin value: [AST or ALT > 2 × baseline AND > 3.0 × ULN] OR [AST or ALT > 8.0 x ULN], combined with [TBIL > 2 × baseline AND > 2.0 × ULN] without evidence of cholestasis
Gastrointestinal	• Nausea and vomiting ≥ Grade 3 for > 3 days despite optimal anti-emetic therapy. • ≥ Grade 3 diarrhea for > 5 days despite optimal antidiarrheal treatment (which could include steroids).
Pancreas	• Symptomatic serum amylase or lipase elevation, medical intervention required (Pancreatitis Grade 3 or higher)
Hypertension	• ≥ Grade 3 hypertension related to the study medication if it persists > 7 days despite optimal anti-hypertensive treatment • Grade 4 hypertension of any duration
Cardiac	• ≥ Grade 3 cardiac event that is symptomatic or requires medical intervention
Pneumonitis	• Grade 2 pneumonitis if it persists > 7 days despite treatment with corticosteroids. • ≥ Grade 3 pneumonitis of any duration
Immune-related toxicities (except pneumonitis)	• Grade 3 immune-related toxicities that persist > 14 days with same severity despite treatment with corticosteroids. • Grade 4 immune related toxicities of any duration • ≥ Grade 3 infusion related reaction
Other Adverse Events	Other clinically significant adverse events: • ≥ Grade 3 adverse events that has not been previously identified for pembrolizumab/platinum-based doublet chemotherapy and/or canakinumab.

TOXICITY	DLT CRITERIA (NCI CTCAE v5.0 will be used for grading)
	• ≥ Grade 3 AEs that are known to occur with pembrolizumab/platinum-based doublet chemotherapy and/or canakinumab, but cannot be controlled using the recommended product-specific management guidelines or leads to <50% of planned exposure of study medications • Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay of > 12 weeks should be considered to be DLTs by the Investigators and Novartis, even if not Grade 3 or higher.
Events which will NOT be considered as DLT for the purpose of this protocol:Clinically insignificant laboratory values ≤ Grade 2. For laboratory values ≥ Grade 3, the maximum allowable time limit for correction of electrolyte abnormalities to ≤ Grade 1 is 72 hr. Events secondary to disease progression and concomitant medications should not be considered DLTs. Decision about RP3R will be made by Dose Level Review Team (DLRT) based on a synthesis of all relevant data available from all dose levels evaluated in the ongoing study including safety information, DLTs , all CTCAE v5.0 Grade ≥ 2 toxicity, PK, and PD data during the first 42 days of combination treatment from evaluable subjects. *Subjects taking paclitaxel can take more than 10 days to recover neutrophils count to > 1000/ mm ^{3} (Lalami et al 2006) # Subjects taking paclitaxel can take~4-6 days to recover from thrombocytopenia (Kuter 2015).	

6.5.3 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule, dose change are permitted and must follow the following principles:

- Canakinumab dose reductions are not permitted, only increase in the dosing interval is allowed (from Q3W to Q6W and from Q6W to Q9W only). Once the dosing interval is increased it cannot be reverted to the previous dosing interval (Section 6.5.3.1).
- Pembrolizumab and chemotherapy agents (carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and pemetrexed) will follow locally approved labels (if pembrolizumab is not yet approved in your country, refer to Section 16.7 and local clinical practice.
- If the chemotherapy drugs need to be interrupted due to toxicity, canakinumab/matching-placebo and pembrolizumab must also be interrupted.
- If pembrolizumab or canakinumab/matching-placebo are interrupted due to toxicity, the other agents may also be interrupted, per investigator discretion.
- Reduction of one chemotherapy agent and not the other agent is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the treatments.
- Pembrolizumab may be interrupted for a maximum of 12 weeks.
- If one of the study drugs is permanently discontinued the other study drugs ongoing can be continued, for treatment beyond RECIST 1.1 disease progression refer to Section 6.1.4.1.

All dose changes in any study drugs must be recorded on the appropriate eCRF page.

6.5.3.1 Guidelines for mandatory dose modifications for canakinumab/matching-placebo

Mandatory dose interruption or discontinuation of canakinumab/matching-placebo in the management of adverse reactions are summarized in Table 6-9. Clinical judgment of the treating physician should guide the management plan of each subject based on individual benefit/risk assessment. However, for events requiring a discontinuation in Table 6-9, canakinumab/matching-placebo must be discontinued. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose

adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity).

If pembrolizumab and all other study chemotherapy drugs are permanently discontinued because of unacceptable toxicities, the investigator can continue canakinumab/ matching-placebo alone until RECIST 1.1 disease progression (Section 6.1.4). If canakinumab is interrupted for more than 12 weeks or a subject misses more than two doses of canakinumab/matching placebo due to canakinumab -related toxicities (whichever is longer), canakinumab/matching placebo must be permanently discontinued.

Unscheduled local laboratory assessments may be performed if medically indicated to document a (potential) adverse event or when the treating physician cannot wait for central laboratory results for decision making (e.g. dose modifications). In this particular situation, if possible, the blood sample obtained at the same timepoint should be submitted to the central laboratory for analysis in parallel with local analysis.

Table 6-9 Criteria for mandatory dose interruption and re-initiation for canakinumab/matching-placebo for adverse drug reactions

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ matching-placebo**
General guidance for adverse events considered to be related to canakinumab (to be followed whenever no other specific guidance is described in this table)	
Grade 1/ Grade 2	Maintain dose level
Grade 3	Interrupt dose until resolved to ≤ Grade 2, then increase canakinumab/matching-placebo dosing interval[a]
Grade 4	Permanently discontinue canakinumab/matching-placebo
Exceptions to the above general guidance[g]	
Neutropenia (ANC)	
Grade 2 (ANC < 1500 - 1000/mm^3)	Interrupt until grade 1 or less then maintain dose
Grade 3 (ANC < 1000 - 500/mm^3)/ Grade 4 (ANC < 500/mm^3)	Interrupt until resolved to ≤ Grade 1, then: • For subjects receiving chemotherapy, maintain canakinumab/matching-placebo dosing interval, only delay canakinumab dose to match chemotherapy dosing • After permanent discontinuation of chemotherapy, increase canakinumab/matching-placebo dosing interval.[a]
Grade 4 (ANC < 500/mm^3) for >7 consecutive days. For paclitaxel/ nab-paclitaxel combinations: for > 14 days	Permanently discontinue canakinumab/matching-placebo
Grade 4 Febrile neutropenia	
• Permanently discontinue canakinumab/matching-placebo	
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Interrupt dose until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7, permanently discontinue canakinumab/matching-placebo
Serum creatinine	
Grade 3	Interrupt dose until resolved to ≤ Grade 2 or baseline, then re-start at the same dose

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ matching-placebo**
	• If not resolved within 14 days, then permanently discontinue canakinumab/matching-placebo
Isolated total bilirubin elevation[b]	
Any elevation > ULN:	• Fractionate bilirubin, evaluate for cholestatic liver injury (ALP) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to local institutional guidelines.
Grade 2 > 1.5 - 3.0 x ULN	• Maintain treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline.
Grade 3 > 3.0 - 10.0 x ULN[c]	Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then increase canakinumab/matching-placebo dosing intervals[a]
Grade 4 > 10.0 x ULN[c]	• see footnote[f] - otherwise discontinue study treatment
Isolated AST or ALT elevation[b]	
With normal baseline AST/ALT:	
Grade 1 > ULN - 3.0 x ULN	Maintain dose level
Grade 2> 3.0 - 5.0 x ULN	Maintain dose level. Repeat LFTs within 48-72 h; if still abnormal then monitor LFTs at least weekly, until resolved to ≤ 3.0 x ULN [e]
Grade 3: AST or ALT > 5.0 - 10.0 x ULN	Interrupt dose. Repeat LFTs within 48-72 h; monitor LFTs at least weekly, until resolved to ≤ 3.0 x ULN. Then: • If resolved in ≤ 14 days, maintain dose level • If resolved in > 14 days, then increase canakinumab/matching-placebo dosing intervals[a].
Grade 3: AST or ALT > 10.0 - 20.0 x ULN	Interrupt canakinumab/matching-placebo. Repeat LFTs within 48-72 h; monitor LFTs at least weekly until resolved to ≤ baseline, then increase canakinumab/matching-placebo dosing intervals [a.].
Grade 4: AST or ALT > 20.0 x ULN	Discontinue canakinumab/matching-placebo. Repeat LFTs within 48-72 h; monitor LFTs at least weekly until resolved to ≤ baseline.
With abnormal baseline ALT/AST (up to Grade 1: ≤ 3.0 x ULN):	
• ALT/AST > 2.0 x baseline AND > 5.0 x ULN	• Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to baseline. If resolved in ≤ 14 days, maintain dose level; if resolved in > 14 days, increase canakinumab/matching-placebo dosing intervals [a.]
• ALT/AST > 3.0 x baseline AND >10 x ULN	• Interrupt treatment. Repeat LFTs within 48-72 hours, then monitor weekly until resolved to baseline, then increase canakinumab/matching-placebo dosing intervals [a.]
• Grade 4: AST or ALT (>20 x ULN)	• Permanently discontinue study treatment.
AST/ALT increase associated with concomitant total bilirubin increase[b]	
With normal baseline LFTs:	

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule modifications for canakinumab/ matching-placebo**
AST or ALT (>3.0xULN) associated with concomitant total bilirubin >2.0 x ULN without evidence of cholestasis[d] (unless Gilbert syndrome)	Interrupt study treatment. Assess if case is true DILI.[f] **If DILI confirmed** - Permanently discontinue **If Not DILI** – interrupt treatment. Treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, till enzyme levels resolve to ≤Grade 1 or Baseline. *Refer to Section 6.5.4.2 for additional follow-up of potential drug induced liver injury cases as applicable.
With abnormal baseline LFTs:	
ALT or AST >3 x baseline ,OR ALT or AST >8 x ULN {whichever is lower] combined with total bilirubin >2.0x ULN	After recovery, re-administration of study treatment could be considered only if Investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of study drug/s and dose regimen, should be discussed with the Novartis medical and safety team. Refer to Section 6.5.4.2 for additional follow-up evaluations as applicable.
Pancreatitis	
Grade 3	• If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then discontinue canakinumab/matching-placebo
Hypertension	
Grade 3	Interrupt dose until resolved ≤ Grade 1, then maintain dose level
Diarrhea - institute appropriate anti-diarrheal treatment and follow general guidelines	
Rash/photosensitivity - initiate/institute appropriate skin toxicity therapy (such as antihistamines and/or topical corticosteroids) and follow general guidelines	
Steven Johnson Syndrome, Toxic epidermal necrolysis	
• Permanently discontinue canakinumab/matching-placebo	
Tuberculosis or reactivation of hepatitis	
• Permanently discontinue canakinumab/matching-placebo	
Asymptomatic laboratory abnormalities- Provide supportive care and replacement therapy	
• If clinically significant, follow general guidelines	

LFTs- Liver function Tests

[a] canakinumab/matching placebo dosing interval can be increased from Q3W to Q6W or from Q6W to Q9W.

[b] Refer to protocol Section 6.5.4.2 for monitoring of liver toxicity.

[c] If total bilirubin > 3.0 x ULN is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines continue treatment at the discretion of the investigator.

[d]The subject should be monitored biweekly (including LFTs), or more frequently if clinically indicated, until total bilirubin have resolved to baseline or stabilization over 4 weeks.

[e]Subject with liver metastasis and baseline values between 3 and 5 x ULN are excluded from repeat assessment

Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any ≥ Grade 3 of amylase and/or lipase.

[f] An isolated bilirubin elevation is not typical for drug-induced liver injury. Bilirubin can be elevated either as part of a “Hy’s law” constellation with a preceding elevation of ALT/AST, or as part of a cholestatic reaction with simultaneous elevation of other cholestatic parameters (ALP, GGT). Isolated bilirubin can be seen in conjunction with drugs that inhibit bilirubin conjugation or excretion, but both scenarios do not typically represent liver injury. Alternative causes of bilirubin elevation should therefore, be ruled out before basing dose modification decisions on bilirubin values alone.

[g]If relatedness to canakinumab can be excluded with certainty and there is no risk for the patient (e.g. creatinine in a subject taking cisplatin), the dose modification for canakinumab is not mandatory

6.5.4 Follow-up for toxicities

6.5.4.1 Follow up for infections

Infections are the most common adverse event observed with canakinumab treatment. Subjects should be followed closely for signs or symptoms of infection and receive prompt appropriate treatment for suspected infections. Subjects will have a urinalysis performed at screening and on Day 1 of every cycle.

6.5.4.2 Follow up on potential drug-induced liver injury (DILI) cases

DILI Diagnosis

Subjects with transaminases elevations combined with total bilirubin (TBIL) increase may be indicative of potentially severe drug-induced liver injury (DILI). These events should be considered as clinically important and should be assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the subject's baseline AST/ALT and TBIL value (Table 6-8 in Section 6.5.3). Subjects meeting any of the following criteria will require further follow-up and assessments as outlined below:

- For subjects with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN
- For subjects with elevated AST or ALT or TBIL value at baseline: [AST or ALT > 3 x baseline] or 8 x ULN, whichever is lower combined with [TBIL > 2 x baseline AND > 2.0 x ULN]

As DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before the diagnosis of DILI is confirmed.

Hepatic toxicity monitoring includes the following LFTs: albumin, ALT, AST, total bilirubin, direct and indirect bilirubin, alkaline phosphatase (fractionated if alkaline phosphatase is grade 2 or higher), creatine kinase, prothrombin time (PT) or INR and gamma-glutamyltransferase (GGT). For subjects with Gilbert Syndrome: total and direct bilirubin must be monitored, intensified monitoring applies to changes in direct bilirubin only.

Evaluate status of liver metastasis (new or exacerbation) or vascular occlusion – CT, MRI, duplex sonography.

Perform relevant examinations (Ultrasound or MRI, ERCP) as appropriate, to rule out if liver test elevations (LFTs) are caused by cholestasis (defined as: ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of alkaline phosphatase (ALP) liver fraction in subjects with bone metastasis).

Note: (The R value is calculated by dividing the ALT by the ALP, using multiples of the ULN for both values. It denotes whether the relative pattern of ALT and/or ALP elevation is due to cholestatic (R≤ 2), hepatocellular (R ≥ 5), or mixed (R >2 and < 5) liver injury).

Table 6-10 provides guidance on specific clinical and diagnostic assessments to be (OR which can be) performed to rule out possible alternative causes of the observed LFT abnormalities.

Table 6-10 Guidance on specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	IgM anti-HAV; HBsAg, IgM & IgG anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	Ultrasound or MRI
Hypoxic/ischemic hepatopathy	Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	Ultrasound or MRI, ERCP as appropriate.
Wilson disease (if <40 yrs old)	Ceruloplasmin
Hemochromatosis	Ferritin, transferrin
Alpha-1-antitrypsin deficiency	Alpha-1-antitrypsin

Other causes should also be considered based upon patients' medical history (Hyperthyroidism / thyrotoxic hepatitis – T3, T4, TSH; CVD / Ischemic hepatitis – ECG, prior hypotensive episodes; T1D / glycogenic hepatitis).

Following appropriate causality assessments, as outlined above, the causality of the drug is estimated as "probable" i.e. >50% likely, if it appears greater than all other causes combined. The term "drug-induced" indicates *probably caused* by the drug, not by something else, and only such a case can be considered DILI case and should be reported as an SAE.

All cases confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant," and thus, meet the definition of SAE and should be reported as SAE using the term "potential treatment-induced liver injury". All events should be followed up with the outcome clearly documented.

DILI Management

In the absence of cholestasis, these subjects should be immediately discontinued from study drug treatment, and repeat Liver Function Tests (LFT) within 48 hours. The evaluation should include laboratory tests, detailed history, physical assessment, and the possibility of liver metastasis or new liver lesions, obstructions/compressions, etc.

Close observation is recommended in case of AST, ALT, and/or bilirubin increase requiring dose interruption, which involves:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or return to normal values.
- Obtaining a more detailed history of current symptoms.
- Obtaining a more detailed history of prior and/or concurrent diseases, including history of any pre-existing liver conditions or risk factors.
- Obtaining a history of concomitant drug use (including non-prescription medications, herbal and dietary supplements), alcohol use, recreational drug use, and special diets.

- Ruling out acute viral hepatitis types A, B, C, D, and E; hepatotropic virus infections (CMV, EBV, or HSV); autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.
- Assessing cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure as possible etiologies for liver dysfunction.
- Obtaining a PK sample, as close as possible to last dose of study drug, to determine exposure to study drug, if PK analysis is performed in the study.
- Considering a liver biopsy, as clinically indicated to assess pathological change and degree of potential liver injury

These assessments should be done in addition to the assessments of immunological markers and total bile acids described in Section 8 .

All cases of DILI confirmed on repeat testing meeting the laboratory criteria defined above, with no other alternative cause for LFT abnormalities identified, should be considered as "medically significant", thus meeting the definition of SAE (Section 10.1.2), and must be reported as SAE using the term "potential drug-induced liver injury". All events must be followed up with the outcome clearly documented. Results of tests as well as other clinically important information will be recorded in the eCRF.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Every time the study treatment is to be administered, IRT must be accessed to assign a medication (kit) number (for the investigational drug canakinumab or canakinumab matching-placebo) and/or registration of the other study drugs dispensed to the subjects. The date and time of all study treatment administrations during the study and any deviations from the protocol treatment schedule will be captured by the investigator staff or by field monitor on the appropriate study treatment dispensing form.

Exposure to the study treatment will be based on the number of injections or infusions administered. Compliance with the study treatment will be assessed by the field monitor at each visit and information provided by the pharmacist or by the investigator.

6.6.2 Emergency breaking of assigned treatment code

Emergency unblinding procedures must only be undertaken when it is required to in order to treat the subject safely.

Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT system. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested

subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- Protocol number
- Study drug name (if available)
- Subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

Study treatment must be discontinued once emergency unblinding has occurred. The subject will have an End of Treatment (EOT) visit completed and will continue to be followed for recurrence as specified in the protocol.

Following unblinding of the investigational sites to treatment allocation (Section 3), this section will no longer be applicable as there will be no need for emergency unblinding.

6.7 Preparation and dispensation

Canakinumab or canakinumab matching-placebo (investigational drug):

Each study site will be supplied by Novartis with the investigational drug in packaging of identical appearance per product volume. Canakinumab in ready for use pre-filled syringes does not require preparation. Canakinumab as solution for s.c injection in vial, which will be used post implementation of protocol amendment 06, requires preparation. For further information on canakinumab injection, please refer to Instruction for use Canakinumab manuals.

Post trial unblinding on 25-Oct-2021, canakinumab-matching placebo was no longer supplied nor dispensed.

For more details, please refer to Section 6.1.

Investigator staff will identify the investigational drug packages for the subject at each dispensing visit by contacting the IRT and obtaining the medication (kit) number.

Other study drugs (pembrolizumab, cisplatin, carboplatin, paclitaxel, nab-paclitaxel and pemetrexed):

The other study drugs (pembrolizumab, pemetrexed, cisplatin, carboplatin, paclitaxel, and nab-paclitaxel) will be supplied locally as commercially available by the site pharmacy or by Novartis, if so, the drugs will be labeled accordingly to comply with the country legal requirements. Preparation and dispensation should follow the locally approved label and local practice.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study drugs supplied by Novartis must be received by a designated person 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, all study drugs must be stored according to the instructions specified on the labels and in the [Investigator's Brochure] for the investigational drug or as per the locally approved label and local practice for the other study drugs. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. Also, for drugs sourced by Novartis, they will include storage conditions for the study treatment but no information about the subject, except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study drugs in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits and at the completion of the trial. At the conclusion of the study, and as appropriate during the course of the study, the investigator will return 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.

The study drugs supply can be destroyed at the local Novartis facility or third party, as appropriate, or locally at the site only if permitted by local regulations and authorized by Novartis.

6.7.1.2 Handling of additional treatment

Not applicable.

6.7.2 Instruction for prescribing and taking study treatment

Refer to Section 6.1.1.1 and Section 6.1.1.2.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/ Institutional Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators, in a separate document, a proposed informed consent form that complies with the International Conference on Harmonization Good Clinical Practices (ICH GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) and/or Core Data Sheet (CDS) for marketed drugs. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN) or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential and female partners of male participants must be informed that taking the study treatment 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 requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

The study includes optional biomarker sample collections and assessments, the option to continue study treatment beyond RECIST 1.1 disease progression and, in some cases, the option to continue study treatment beyond iRECIST iCPD. These will require a separate signature if the subject agrees to participate. It is required as part of this protocol that the investigator presents these options to the subjects, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments will in no way affect the subject’s ability to participate in the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial subject and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The assessment schedules Table 8-2 Safety run-in part, Table 8-3 Double-blind, randomized, placebo-controlled part, Table 8-4 Open label extension and Table 8-5 Post implementation of protocol amendment 05, list all of the assessments and indicates with an "X", the visits when they are performed and with an "S", the visit when they are to be documented in the subject source medical record only. All data obtained from these assessments must be supported in the subject's source documentation.

Treatment cycles are intended to be 3 weeks (21 days), but the treatment can be delayed in order to manage toxicities according to the canakinumab/matching-placebo dose modification criteria in Section 6.5.3 and the locally approved label and local practice for the other study drugs. In such cases, all study procedures (except imaging) will be completed at a later date corresponding to the delayed treatment. Imaging will be performed every 6 weeks (for the first 12 weeks) starting from Cycle 1 Day 1 regardless of any treatment delays. Tumor assessments post week 12 are specified in Table 8-2, Table 8-3, Table 8-4, Table 8-5 and in Section 8.3. During the course of the study visits, test procedures should occur on schedule whenever possible as per allowable visit windows specified in Table 8-1 below.

Note: If any drug of the study treatment is temporarily interrupted or permanently discontinued at any time during the study, efficacy assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments.

Table 8-1 Allowable visit windows are specified as follows:

Visit name	Window
Screening	-28 Days
All assessments including C1D1, during the treatment period (except tumor assessments)	± 3 Days
Canakinumab or canakinumab matching-placebo injection (if applicable)	± 3 Days
Pembrolizumab infusion (if applicable)	± 3 Days
Chemotherapies infusion (if applicable)	± 3 Days
PK/IG/PD sampling	Refer to tables in Section 8.5.2
Tumor assessments	± 7 Days
26 day safety follow-up visit	± 7 Days
52, 78, 104-day safety follow-up visits	± 7 Days
130-day safety follow-up visit	+ 14 Days
EOT	≤ 7 Days after permanent discontinuation of study treatment
Survival follow- up	± 7 Days

Every effort must be made to follow the schedule of assessments within the windows outlined in Table 8-2, Table 8-3,Table 8-4 and Table 8-5, as applicable. If an off-schedule imaging assessment is performed, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Additional assessments may be performed as clinically indicated.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as

possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the appropriate eCRF.
All data obtained from these assessments must be supported in the subject's source documentation.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local Health Authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the subject´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the subject to visit the site again. If the Investigator delegates tasks to an off-site healthcare professional, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 8-2 Assessment Schedule, Safety run-in part

Period		**Induction**										**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**		
Main informed consent	X																					
IRT Screening (after ICF signature)	X																					
IRT Enrollment		X																				
Collection of concomitant molecular alteration data (EGFR/ALK)	S																					
Archival or newly obtained tumor sample for ALK/EGFR testing by Novartis designated laboratory (if no local testing available)	X																					
Demography	X																					
Inclusion / Exclusion criteria	X																					
Medical history/current medical conditions	X																					
Diagnosis, stage and grade of cancer	X																					
Smoking history	X																					
Prior/concomitant medications	From 28 days prior to first dose until 130 days after EOT or start of new antineoplastic drugs, whichever is sooner. After starting a new antineoplastic drug, only report concomitant medications for AEs/SAEs suspected to be related to any study drugs.																					
Non-drug therapies and procedures	From 28 days prior to first dose until 130 days after EOT or start of new antineoplastic drugs, whichever is sooner. After starting a new antineoplastic drug, only report non-drug therapies for AEs/SAEs suspected to be related to any study drugs.																					

Period		**Induction**										**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**		
Prior anti-neoplastic therapies (medications, surgery, radiotherapy)	X																					
Physical Examination	S	S				S		S		S		S		S	S	S		S		S		
ECOG performance status	X	X				X		X		X		X		X	X	X		X		X		
Body Height	X																					
Body Weight	X	X				X		X		X		X		X	X	X		X		X		
Vital Signs	X	X				X		X		X		X		X	X	X		X		X		
Determination of tuberculosis status	S																					
HIV history (HIV testing where locally required)	S																					
Hematology	X	X			X	X	X	X	X	X	X	X		X	X	X		X		X		
Blood Chemistry	X	X			X	X	X	X	X	X	X	X		X	X	X		X		X		
Coagulation	X	If clinically indicated																				
Total T3, FT4 and TSH	X	X						X				X		To be repeated every other Cycle beginning with Cycle 7	X	X						
Hepatitis testing	X	If clinically indicated																				
Urinalysis	X	X				X		X		X		X		X	X	X		X		X		
Serum pregnancy test	X														X[1]							
Urine pregnancy test[1]		S				S		S		S		S		S		S		S		S		
CT or MRI of Chest and Abdomen (with intravenous contrast enhancement)[2]	X	Every 6 weeks (for the first 12 weeks), then every 9 weeks through week 75 and every 12 weeks thereafter[3]																				
Brain CT or MRI[2]	X	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																				

Period		**Induction**										**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**		
Whole body bone scan[2]	X	If clinically indicated																				
CT scan or MRI of other metastatic sites (e.g., neck, pelvis, etc.)[2]	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																				
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole body bone scan that are not visible on the chest/abdomen and pelvis, if applicable, CT or MRI)[2]	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																				
Photography (for any skin lesion)[2]	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																				
Electrocardiogram (ECG)[4]		X[5]												C6D1[5]								
Adverse Events	Continuous, up to 130 days after last dose of study treatment or start of new post study treatment antineoplastic medication (whichever is sooner)																					
Serious Adverse Events	Continuous, up to 130 days after last dose of study treatment or start of new post study treatment antineoplastic medication (whichever is sooner)																					SAEs related to study treatment[8]
Drug administration[6]		X				X		X		X		X		X								
IRT drug discontinuation															X							
Canakinumab PK sampling[7]		X	X	X	X	X		X		X		X	X	C6D1, C8D1, C12D1, C16D1	X	X		X		X		

Period		**Induction**										**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**15**	**1**	**15**	**1**	**15**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**		
Canakinumab Immunogenicity sampling[7]		X								X				C8D1, C12D1, C16D1	X	X		X		X		
Canakinumab Pharmacodynamic / Total IL-1β[7]		X			X							X		C16D1	X	X		X		X		
Pembrolizumab PK sampling[7]		X	X	X	X	X		X		X		X		C6D1, C8D1, C12D1, C16D1	X	X						
Pembrolizumab Immunogenicity sampling[7]		X				X				X				C8D1, C12D1, C16D1	X	X						
Pemetrexed PK sampling[7]		X				X																
Cisplatin PK sampling[7]		X				X																
Carboplatin PK sampling[7]		X				X																
Paclitaxel PK sampling[7]		X				X																
Antineoplastic therapies since discontinuation of study treatment																At every visit (on site or phone call) during safety follow up, efficacy follow up and survival follow up.						
Disposition Assessment	X														X						X	
Survival Follow-up																						X

Period	Induction										Maintenance				Follow-up						
Visit Name	Screening	Cycle 1				Cycle 2		Cycle 3		Cycle 4		Cycle 5		Subsequent Cycles	EOT	Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)					End of post treatment follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	8	15	1	15	1	15	1	15	1	8	Day 1 (or as reported)	-	1	2	3	4	5		

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] For women with child bearing potential status confirmed only. For further details please refer to Section 8.4.5
[2] For further details please refer to Section 8.3 Efficacy assessments
[3] Tumor assessment at end of treatment (EOT) only for subjects without documented RECIST 1.1 PD and who do not enter the efficacy follow-up phase provided the last scan was not conducted within 30 days prior to the end of study treatment.
[4] For further details please refer to Section 8.4.4 Electrocardiogram (ECG)
[5] Pre-dose
[6] For further details refer to Section 6.1 Study Treatment. From Cycle 5 onward only canakinumab, pembrolizumab and pemetrexed (for non-squamous subjects only) to be administered.
[7] For further details refer to specifying table in Section 8.5.2 Pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamics (PD) assessments
[8] Until study completion and regardless of any new therapies

Table 8-3 Assessment Schedule, Double-blind, randomized, placebo-controlled part

Period		**Induction**								**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**1**	**1**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**
Main informed consent	X																			
Optional pharmacogenetic informed consent	X																			
IRT Screening (after ICF signature)	X																			
IRT randomization		X																		
Collection of concomitant molecular alteration data (EGFR/ALK)	S																			
Archival or newly obtained tumor sample for PD-L1 testing by Novartis designated laboratory (and for ALK/EGFR if no local testing available)	X																			
Demography	X																			
Inclusion / Exclusion criteria	X																			
Medical history/current medical conditions	X																			
Diagnosis, stage and grade of cancer	X																			
Smoking history	X																			
Prior/concomitant medications	From 28 days prior to first dose until 130 days after EOT or start of new antineoplastic drugs, whichever is sooner. After starting a new antineoplastic drug, only report concomitant medications for AEs/SAEs suspected to be related to any study drugs.																			
Non-drug therapies and procedures	From 28 days prior to first dose until 130 days after EOT or start of new antineoplastic drugs, whichever is sooner. After starting a new antineoplastic drug, only report non-drug therapies for AEs/SAEs suspected to be related to any study drugs.																			

Period		**Induction**								**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**1**	**1**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**
Prior anti-neoplastic therapies (medications, surgery, radiotherapy)	X																			
Physical Examination	S	S				S		S	S	S		S	S	S		S		S		
ECOG performance status	X	X				X		X	X	X		X	X	X		X		X		
Body Height	X																			
Body Weight	X	X				X		X	X	X		X	X	X		X		X		
Vital Signs	X	X				X		X	X	X		X	X	X		X		X		
Determination of tuberculosis status	S																			
HIV history (HIV testing where locally required)	S																			
Hematology	X	For all subjects: on Day 1 and 15; only for subjects on nab-paclitaxel: Day 1, Day 8 and Day 15								X		X	X	X		X		X		
Blood Chemistry	X	For all subjects: on Day 1 and 15; only for subjects on nab-paclitaxel: Day 1, Day 8 and Day 15								X		X	X	X		X		X		
Coagulation	X	If clinically indicated																		
Total T3, FT4 and TSH	X	X						X		X		To be repeated every other Cycle beginning with Cycle 7	X	X						
Hepatitis testing	X	If clinically indicated																		
Urinalysis	X	X				X		X	X	X		X	X	X		X		X		
Serum pregnancy test	X												X[1]							
Urine pregnancy test[1]		S				S		S	S	S		S		S		S		S		

Period	Screening	Induction								Maintenance				Follow-up							
Visit Name		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5		Subsequent Cycles	EOT	Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)					End of post treatment follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	8	15	1	2	1	1	1	8	Day 1 (or as reported)	-	1	2	3	4	5	-	-
CT or MRI of Chest and Abdomen (with intravenous contrast enhancement)[2]	X	Every 6 weeks (for the first 12 weeks), then every 9 weeks through week 75 and every 12 weeks thereafter[3]																		
Brain CT or MRI[2]	X	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																		
Whole body bone scan[2]	X	If clinically indicated																		
CT scan or MRI of other metastatic sites (e.g., neck, pelvis, etc.)[2]	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																		
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole body bone scan that are not visible on the chest/abdomen and pelvis, if applicable, CT or MRI)[2]	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																		
Photography (for any skin lesion)[2]	If clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen																		
Electrocardiogram (ECG)[4]		X[5]																		
Electronic patient reported outcomes (ePRO)[6]		Day 1 of each cycle; at the End of Treatment (EOT) visit; before tumor assessments during efficacy follow-up (See Table 8-4); and 7 and 28 days post progression per RECIST 1.1 as per Investigator.																		
Adverse Events	Continuous, up to 130 days after last dose of study treatment or start of new post study treatment antineoplastic medication (whichever is sooner)																			
Serious Adverse Events	Continuous, up to 130 days after last dose of study treatment or start of new post study treatment antineoplastic medication (whichever is sooner)																			SAEs related to study treatment[15]
Drug administration[7]		X				X		X	X	X		X								

Period		**Induction**								**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**1**	**1**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**
Nab-paclitaxel Drug administration[7]		Only for subjects on nab-paclitaxel: administration on Day 1, Day 8, and Day 15 at each cycle																		
IRT drug discontinuation													X							
Optional Newly obtained tumor sample on treatment[8,14]								Anytime between C3D1 and C3D15												
Optional Newly obtained tumor sample at confirmed disease progression[8,14]		At time of confirmed disease progression and prior to the start of new antineoplastic therapy																		
Blood (serum) for hs-CRP testing[8,9, 14]		X				X		X	X	X		C12D1, C16D1	X	X[10]		X[10]		X[10]		
Blood (plasma) for cytokine testing[8,11, 14]		X				X		X	X	X		C12D1, C16D1	X	X[10]		X[10]		X[10]		
Optional unscheduled blood (plasma) for cytokine analysis (and soluble circulating markers)[11,14]		In case of suspected immune-related adverse event observed																		
Blood (plasma) for circulating tumor DNA (ctDNA)[8,11,14]		X								X		C8D1, C12D1	X							
Blood for circulating tumor cells (CTC)[12, 14]		X																		
Optional Blood for pharmacogenetic analysis (PG informed consent is required) [14]		X																		
Canakinumab PK sampling[13]		X	X	X	X	X		X	X	X	X	C6D1, C8D1, C12D1, C16D1	X	X		X		X		

Period		**Induction**								**Maintenance**				**Follow-up**						
Visit Name	**Screening**	**Cycle 1**				**Cycle 2**		**Cycle 3**	**Cycle 4**	**Cycle 5**		**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Days	**-28 to -1**	**1**	**2**	**8**	**15**	**1**	**2**	**1**	**1**	**1**	**8**	**Day 1 (or as reported)**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**
Canakinumab Immunogenicity sampling[13]		X							X			C8D1, C12D1, C16D1	X	X		X		X		
Canakinumab Pharmacodynamic / Total IL-1β[13]		X			X					X		C16D1	X	X		X		X		
Pembrolizumab PK sampling[13]		X	X	X	X	X		X	X	X		C6D1, C8D1, C12D1, C16D1	X	X						
Pembrolizumab Immunogenicity sampling[13]		X				X			X			C8D1, C12D1, C16D1	X	X						
Pemetrexed PK sampling[13]		X				X														
Cisplatin PK sampling[13]		X				X														
Carboplatin PK sampling[13]		X				X														
Paclitaxel PK sampling[13]		X				X	X													
nab-Paclitaxel PK sampling[13]		X				X	X													
Antineoplastic therapies since discontinuation of study treatment														At every visit (on site or phone call) during safety follow up, efficacy follow up and survival follow up.						
Disposition Assessment	X												X						X	
Survival Follow-up																				X

Period	Screening	Induction								Maintenance				Follow-up							
Visit Name		Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5		Subsequent Cycles	EOT	Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)					End of post treatment follow-up	Survival follow-up (every 12 weeks)
Days	-28 to -1	1	2	8	15	1	2	1	1	1	8	Day 1 (or as reported)	-	1	2	3	4	5	-	-

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] For women with child bearing potential status confirmed only. For further details please refer to Section 8.4.5
[2] For further details please refer to Section 8.3 Efficacy assessments
[3] Tumor assessment at end of treatment (EOT) only for subjects without documented RECIST PD and who do not enter the efficacy follow-up phase provided the last scan was not conducted within 30 days prior to the end of study treatment.
[4] For further details please refer to Section 8.4.4 Electrocardiogram (ECG)
[5] Pre-dose
[6] ePRO questionnaires should be completed prior to all other assessments in the Assessment Schedule. For further details please refer to Section 8.5.1 Clinical Outcome Assessments (COA).
[7]For further details please refer to Section 6.1 Study Treatment. From Cycle 5 onward only canakinumab/matching placebo, pembrolizumab and pemetrexed (for non-squamous subjects only) to be administered.
[8] Also to be collected as unscheduled, if needed and at time of confirmed disease progression
[9] (5 mL) of whole blood will be collected for hs-CRP. For further details please refer to Section 8.5.3.2
[10] Only collected prior to start of any new antineoplastic therapy
[11] (10 mL) of whole blood will be collected for each of the following: Cytokines, Unscheduled cytokines at AE, and ctDNA
[12] (10 mL) of whole blood will be collected for CTC. Assessment to be performed only on a subset of subjects, as specified in the protocol.
[13] For further details please refer to Section 8.5.2 Pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamics (PD) assessments
[14] For China only: biomarker tests will not be done unless approval has been obtained by all relevant Chinese authorities
[15] Until study completion and regardless of any new therapies

Table 8-4 Assessment Schedule, Open Label Extension Phase

Period		**Maintenance (Open Label Extension)**		**Follow up**						
Visit Name	**Crossover/ Transition**	**Open Label Extension (OLE) Cycles**	**EOT**	**OLE Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Visits	**-**	**OLE Cycle 1 Day 1 and subsequent OLE cycles**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**
IRT OLE registration	X									
Extension Details CRF completed	X									
Prior/concomitant medications	Continuously collect during the study until 130 days after EOT or start of new antineoplastic drugs, whichever is sooner. After starting a new antineoplastic drug, only report concomitant medications for AEs/SAEs suspected to be related to any study drugs.									
Non-drug therapies and procedures	Continuously collect during the study until 130 days after EOT or start of new antineoplastic drugs, whichever is sooner. After starting a new antineoplastic drug, only report non-drug therapies for AEs/SAEs suspected to be related to any study drugs.									
Physical Examination		S	S	S		S		S		
ECOG performance status		X	X	X		X		X		
Body Weight		Only if clinically indicated	X	X		X		X		
Vital Signs		X	X	X		X		X		
Hematology		On OLE C1D1 and every second cycle thereafter and as clinically indicated Only for subjects on pemetrexed: please monitor labs according to local label	X	X		X		X		
Blood Chemistry		On OLE C1D1 and every second cycle thereafter and as clinically indicated Only for subjects on pemetrexed: please monitor labs according to local label	X	X		X		X		
Coagulation		If clinically indicated								
Total T3, FT4 and TSH		On OLE C1D1[14] and every fourth cycle thereafter and as clinically indicated	X	X						
Hepatitis testing		If clinically indicated								
Serum pregnancy test			X[1]							

Period		**Maintenance (Open Label Extension)**		**Follow up**						
Visit Name	**Crossover/ Transition**	**Open Label Extension (OLE) Cycles**	**EOT**	**OLE Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Visits	**-**	**OLE Cycle 1 Day 1 and subsequent OLE cycles**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**
Urinalysis		On OLE C1D1[14] and every fourth cycle thereafter and as clinically indicated	X	X		X		X		
Urine pregnancy test[1]		S		S		S		S		
CT or MRI of Chest and Abdomen (with intravenous contrast enhancement)[2]		Follow the same schedule as in Table 8-2 (Safety Run In part) or Table 8-3 (Randomized part), as appropriate, until 159 Weeks (approximately 3 years) after the study C1D1; thereafter, every 24 weeks[3].								
Brain CT or MRI[2]		If clinically indicated and/or positive at study baseline, follow same schedule as CT/MRI of chest and abdomen								
Whole body bone scan[2]		If clinically indicated								
CT scan or MRI of other metastatic sites (e.g., neck, pelvis, etc.)[2]		If clinically indicated and/or positive at study baseline, follow same schedule as CT/MRI of chest and abdomen								
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole body bone scan that are not visible on the chest/abdomen and pelvis, if applicable, CT or MRI)[2]		If clinically indicated and/or positive at study baseline, follow same schedule as CT/MRI of chest and abdomen								
Photography (for any skin lesion) [2]		If clinically indicated and/or positive at study baseline, follow same schedule as CT/MRI of chest and abdomen								
Electrocardiogram (ECG)[4]		If clinically indicated								
Electronic patient reported outcomes (ePRO) [5, 15]		Follow the same schedule as for tumor assessments. Also, at the End of Treatment (EOT) visit; before tumor assessments during efficacy follow-up (See Table 8-5); and 7 and 28 days post progression per RECIST 1.1 as per Investigator								
Adverse Events		Continuous, up to 130 days after last dose of study treatment or start of new post study treatment antineoplastic medication (whichever is sooner)								

Period		**Maintenance (Open Label Extension)**		**Follow up**						
Visit Name	**Crossover/ Transition**	**Open Label Extension (OLE) Cycles**	**EOT**	**OLE Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Visits	-	**OLE Cycle 1 Day 1 and subsequent OLE cycles**	-	**1**	**2**	**3**	**4**	**5**	-	-
Serious Adverse Events		Continuous, up to 130 days after last dose of study treatment or start of new post study treatment antineoplastic medication (whichever is sooner)								SAEs related to study treatment [12]
Drug administration[6]		X								
IRT drug discontinuation			X							
Optional newly obtained tumor sample at confirmed disease progression [7,11,15]		At time of confirmed disease progression and prior to the start of new antineoplastic therapy								
Blood (serum) for hs-CRP testing [7,8,11, 15]	X[13]	OLE Cycle 3 Day 1[13]	X	X[9]		X[9]		X[9]		
Blood (plasma) for cytokine testing [7,10,11, 15]	X[13]	OLE Cycle 3 Day 1[13]	X	X[9]		X[9]		X[9]		
Optional unscheduled blood (plasma) for cytokine analysis (and soluble circulating markers) [10,11, 15]		In case of suspected immune-related adverse event observed								
Blood (plasma) for circulating tumor DNA (ctDNA) [7,10,11,15]	X[13]		X							
Antineoplastic therapies since discontinuation of study treatment				At every visit (on site or phone call) during safety follow up, efficacy follow up and survival follow up						
Disposition Assessment			X						X	
Survival Follow-up										X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

[S] Assessment to be recorded in the source documentation only

[1] For women with child bearing potential status confirmed only. For further details please refer to Section 8.4.5

[2] For further details please refer to Section 8.3 Efficacy assessments

Period		**Maintenance (Open Label Extension)**		**Follow up**						
Visit Name	**Crossover/ Transition**	**Open Label Extension (OLE) Cycles**	**EOT**	**OLE Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of post treatment follow-up**	**Survival follow-up (every 12 weeks)**
Visits	**-**	**OLE Cycle 1 Day 1 and subsequent OLE cycles**	**-**	**1**	**2**	**3**	**4**	**5**	**-**	**-**

[3] Tumor assessment at end of treatment (EOT) only for subjects without documented RECIST PD and who do not enter the efficacy follow-up phase provided the last scan was not conducted within 30 days prior to the end of study treatment.

[4] For further details please refer to Section 8.4.4 Electrocardiogram (ECG)

[5] ePRO questionnaires should be completed prior to all other assessments in the Assessment Schedule. For further details, please refer to Section 8.5.1 Clinical Outcome Assessments (COA).

[6] For further details please refer to Section 6.1 Study Treatment.

[7] Also to be collected as unscheduled, at time of confirmed disease progression

[8] 5 mL of whole blood will be collected for hs-CRP. For further details please refer to Section 8.5.3.2

[9] Only collected prior to start of any new antineoplastic therapy

[10] 5 mL of whole blood will be collected for Cytokines and Unscheduled cytokines at AE; 10 mL of whole blood will be collected for ctDNA

[11] **For China only:** biomarker tests will not be done unless approval has been obtained by all relevant Chinese authorities

[12] Until study completion and regardless of any new therapies

[13] Only for patients crossing over from placebo to canakinumab: prior to crossover to canakinumab and on OLE C3D1 for hsCRP and cytokines; only prior to crossover to canakinumab ,for ctDNA

[14] If a test was done at the immediately preceding visit, do not repeat on OLE C1D1.

[15] Not applicable for Safety Run In patients who transition to Open Label Extension phase

Table 8-5 Assessment Schedule, Post implementation of protocol amendment 05

Period	**Maintenance**		**Follow-up**					
Visit Name	**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of follow up**
Days	**Day 1**	**-**	**1**	**2**	**3**	**4**	**5**	
Main informed consent	X							
Prior/concomitant medications	From 28 days prior to first dose until 130 days after EOT							
Non-drug therapies and procedures	From 28 days prior to first dose until 130 days after EOT							
Physical Examination	S	S	S		S		S	
Body Weight	X	X	X		X		X	
Vital Signs	X	X	X		X		X	
Hematology	D1 of every second cycle thereafter and as clinically indicated For subjects on pemetrexed: monitor labs according to local label	X	X		X		X	
Blood Chemistry	D1 of every second cycle thereafter and as clinically indicated For subjects on pemetrexed: monitor labs according to local label	X	X		X		X	
Serum pregnancy test		X[1]						
Urine pregnancy test[1]	S		S		S		S	
CT or MRI of Chest and Abdomen (with intravenous contrast enhancement)[2]	S - Every 12 weeks[3]							
Brain CT or MRI[2]	S - If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							
Whole body bone scan[2]	S - If clinically indicated							
CT scan or MRI of other metastatic sites (e.g., neck, pelvis, etc.)[2]	S - If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole-body bone scan that are not visible on the chest/abdomen and pelvis, if applicable, CT or MRI)[2]	S - If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							

Period	**Maintenance**		**Follow-up**					
Visit Name	**Subsequent Cycles**	**EOT**	**Safety follow-up visit (every 26 d for 130 d after the last dose of the study treatment)**					**End of follow up**
Days	**Day 1**	**-**	**1**	**2**	**3**	**4**	**5**	
Photography (for any skin lesion)[2]	S - If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen							
Electrocardiogram (ECG)[4]	X If clinically indicated							
Adverse Events	Continuous, up to 130 days after last dose of study treatment							
Serious Adverse Events[5]	Continuous, up to 130 days after last dose of study treatment							
Drug administration[6]	X							
IRT drug discontinuation		X						
Disposition Assessment		X						X

X: Assessment to be recorded in the clinical database or received electronically from a vendor

S: Assessment to be recorded in the source documentation only

[1] For women with childbearing potential status confirmed only. For further details please refer to Section 8.4.5 Pregnancy and assessments for fertility

[2] For further details please refer to Section 8.3 Efficacy assessments. Post implementation of Protocol amendment 05, only the RECIST 1.1 response assessment will be recorded in the clinical database. Other efficacy assessment will be recorded in the source documentation only

[3] Tumor assessment at end of treatment (EOT) only for subjects without documented RECIST PD provided the last scan was not conducted within 30 days prior to the end of study treatment

[4] For further details please refer to Section 8.4.4 Electrocardiogram

[5] SAE experienced after the 130-day safety follow-up period should be reported to the Novartis Safety only if the investigator suspects a causal relationship to the study treatment. For further details refer to Section 8.4 Safety and Section 10.1.3 SAE reporting

[6] For further details please refer to Section 6.1 Study Treatment

8.1 Screening

All subjects must provide a signed main ICF prior to performing any study specific procedures. Subjects will be evaluated against all study inclusion and exclusion criteria.

After signing the study ICF, the screening assessments will be done within 28 days prior to enrollment/randomization (Table 8-2 and Table 8-3). Laboratory parameters may be retested within the 28-day screening period for a subject if such parameters meet an exclusion criterion. Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except complete blood count if not done within 7 days prior to the first dose of treatment) unless deemed clinically necessary by investigator and/or required as per local institutional policies.

In the safety run-in part of the study, known PD-L1 status is not required. In part 2 subject randomization will be stratified based on central determination of PD-L1 status and a tumor tissue will be sent to a Novartis designated central laboratory for determination of PD-L1 status prior to randomization, immediately after patient has signed the ICF and no later than Day -14 before randomization.

In addition, EGFR and ALK status must be determined prior to enrollment/randomization for all subjects. Local testing is allowed and results must be documented in the source documents prior to randomization. If local EGFR and ALK testing is not possible, the tumor sample will be tested by the Novartis designated central laboratory.

Imaging assessments will be completed at screening during the regular work-up of the subject within 28 days prior to start of treatment. Imaging done before signing the main study ICF can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

Re-screening is not allowed (subject who was screen-failed cannot sign a new informed consent form (ICF), however, laboratory parameters or other screening parameters may be retested within 28-day screening period for an individual subject).

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.1.1 Eligibility screening

When all screening procedures are completed and the subject's eligibility is confirmed (i.e. all inclusion/exclusion criteria have been verified), the key eligibility criteria checklist embedded in the IRT system will be completed prior to the first dose of study drug.

Please refer to Section 6.3.2 and as well as comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible prior to enrollment/randomization will be considered screen failures. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and inclusion/exclusion eCRF pages must also be completed for screen failure subjects. No

other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event during the screening phase (Section 10.1.2 for reporting details). Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. If the subject fails to be randomized, the IRT must be notified within 2 days.

8.2 Subject demographics/other baseline characteristics

Data to be collected on subject characteristics at screening include:

- Demographic information (age, gender, race and ethnicity as allowed by local regulations).
- Other background or relevant medical history (including smoking history)
- Cancer characteristics including diagnosis, history, extent of cancer, prior anticancer treatments (medications, radiation, surgeries), date of progression prior to study entry
- Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Table 8-2 and Table 8-3 (e.g. ECOG Performance Status, complete physical examination, vital signs, hematology, blood chemistry, coagulation, urinalysis, serum pregnancy test for all female subjects, tumor imaging assessments). Vital signs must include at minimum: heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.
- Prior and current concomitant medications and surgical and medical procedures.
- Tumor imaging assessments - Refer to Table 8-6 .

Data to be collected on Cycle 1 Day 1 pre-dose include:

- Patient Reported Outcomes (PROs)
- 12-Lead Electrocardiogram (ECG)
- Pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamics (PD).

8.3 Efficacy assessments

8.3.1 Tumor assessments

Tumor response will be assessed locally by the investigator according to the Novartis guideline version 3.2 based on RECIST 1.1 (Section 16.1) and iRECIST (Section 16.2). The imaging collection plan is presented in Table 8-6 and is applicable for both study parts (safety run-in part and double-blind, randomized, placebo-controlled part). The local investigator's assessment will be used for primary endpoint analysis (RECIST 1.1) and for treatment decision making based on secondary and exploratory efficacy endpoints (RECIST 1.1 and iRECIST).

For the randomized part, imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO) designated by Novartis. Central review of the imaging data will be performed according to an audit based approach detailed in the Statistical Analysis Plan (SAP) (Section 12.8.1). Further details on the central assessment can be found in the independent review charter of the imaging CRO. Please refer to the site imaging operations manual for additional information on the image acquisition and data collection by the imaging CRO. Imaging data for the OLE phase should not be submitted to the imaging CRO as there will be no central assessment done, only local assessment will be performed in the OLE.

Tumor assessments on study treatment should be scheduled using the C1D1 date as the reference date and continued regardless of study treatment interruption, unscheduled assessments, or transition to the OLE phase. Additional imaging assessments may be performed at any time during the study at the investigator's discretion to support the efficacy evaluations for a subject, as necessary. Clinical suspicion of disease progression at any time requires a physical examination and tumor assessments to be performed promptly rather than waiting for the next scheduled imaging assessment. Each lesion that is measured at baseline must be measured by the same method (either same imaging method or by photography, including a metric ruler) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. Combined Positron Emission Tomography (PET)/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. At the discretion of the investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Section 16.1) and per iRECIST (Section 16.2).

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

Post implementation of protocol amendment 05, only the RECIST 1.1 response assessment will be recorded in the appropriate CRF page. Other efficacy assessments will be recorded in the source documentation only. Also, the efficacy follow-up will no longer be performed.

Table 8-6 Imaging Assessment Collection Plan

Procedure	**Screening/ Baseline**	**Post baseline (during Treatment)**	**Efficacy follow up** (post implementation of protocol amendment 05: not applicable)
CT or MRI of Chest and Abdomen (with intravenous contrast enhancement)	Mandated	Mandated at week 6 and week 12 starting on C1D1, then every 9 weeks (through week 75), every 12 weeks thereafter until progression of disease (PD) as per RECIST 1.1 or transition to OLE. **Study treatment beyond initial RECIST 1.1 PD:** Follow-up scan 4 to 8 weeks after initial iUPD, and then continue tumor assessments using the same schedule until immune confirmed progression by iRECIST (iCPD) or discontinuation of study treatment (whichever occurs earlier). For subjects who discontinue study treatment without iCPD, continuation of tumor assessments until iCPD or start of new anti-neoplastic therapy is recommended **End of Treatment (EOT):** done for all subjects without prior documented RECIST 1.1 PD and who do not enter the efficacy follow-up phase provided the last scan was not conducted within 30 days prior to the end of study treatment	Efficacy Follow-up for progression: continue tumor assessments using the same schedule until RECIST 1.1 PD or death (regardless of start of new anti-neoplastic therapy).

Procedure	**Screening/ Baseline**	**Post baseline (during Treatment)**	**Efficacy follow up** (post implementation of protocol amendment 05: not applicable)
		OLE phase: Follow the same schedule as in Table 8-2 (Safety Run In part) or Table 8-3 (Randomized part), as appropriate, until 159 weeks (approximately 3 years) after the study C1D1; thereafter, every 24 weeks. Post implementation of protocol amendment 05: every 12 weeks until protocol defined patient discontinuation or sponsor study termination.	
Brain CT or MRI	Mandated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Whole body bone scan	Mandated	If clinically indicated	If clinically indicated
CT scan or MRI of other metastatic sites (e.g., neck, pelvis, etc.)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Localized bone CT scan, MRI or x-ray (for any skeletal lesions identified on the whole body bone scan that are not visible on the chest/abdomen , if applicable, CT or MRI)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen
Photography (for any skin lesions)	Only if clinically indicated	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen	If clinically indicated and/or positive at baseline, follow same schedule as CT/MRI of chest and abdomen

8.3.1.1 Baseline imaging assessments

Imaging assessments will be performed at screening/baseline within 28 days of start of treatment (Day -28 to Day -1 prior to Cycle 1 Day 1).

Any imaging assessments already completed during the regular work-up of the subject within 28 days prior to start of treatment, including before signing the main study ICF, can be considered the baseline images for this study. Any imaging assessments obtained after enrollment (subjects in part 1) or randomization (subjects in part 2) cannot be considered baseline images.

Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.

8.3.1.2 Post-baseline imaging assessments

Post-baseline imaging assessments are imaging assessments completed during the study treatment until end of treatment (EOT).

Imaging assessments for response evaluation will be performed at week 6 and week 12 starting on C1D1, then every 9 weeks through week 75, then every 12 weeks thereafter until disease progression per RECIST 1.1, death, lost to follow-up, pregnancy, withdrawal of consent or transition to the OLE phase. During the OLE phase, imaging assessments should follow the same schedule as in the safety run in part (Table 8-2) or the randomized part (Table 8-3), as appropriate, until 159 weeks (approximately 3 years) after the study C1D1; thereafter, every 24 weeks.

If study treatment is continued beyond disease progression as per RECIST 1.1 (Section 6.1.4.1), a follow-up scan after the initial immune unconfirmed RECIST 1.1 progressive disease (iUPD) per iRECIST per investigator should be done within 4 to 8 weeks, then tumor assessment will continue using the same schedule until immune confirmed PD (iCPD) by iRECIST per investigator or until discontinuation study treatment for other reasons (whichever occurs earlier).

For subjects who discontinue study treatment without iCPD, continuation of tumor assessments until iCPD or start of new anti-neoplastic therapy is recommended.

8.3.1.3 End of treatment imaging assessments

At end of treatment, imaging assessments will be done for all subjects without prior documented RECIST 1.1 PD and who do not enter the efficacy follow-up phase provided the last imaging assessments was not conducted within 30 days prior to the end of study treatment.

8.3.1.4 Efficacy follow-up imaging assessments

All subjects who discontinue study treatment **without** prior documented disease progression RECIST 1.1 as per investigator will continue these efficacy imaging assessments, in the efficacy follow-up phase, until documented disease progression by RECIST 1.1 as per investigator, withdrawal of consent, pregnancy, lost to follow up, or death irrespective of start of new anti-neoplastic therapy.

Post implementation of protocol amendment 05, efficacy follow-up will no longer be performed.

8.3.2 Appropriateness of efficacy assessments

Not applicable.

8.3.3 Survival assessments

All subjects will be followed for survival status every 12 weeks regardless of treatment discontinuation reason (except if consent is withdrawn or subject is lost to follow-up) until death,

lost to follow-up, or withdrawal of consent for survival follow-up. Additional survival assessments may be performed outside the 12 weeks follow-up schedules if a survival update is required for an interim assessment to meet safety or regulatory needs. Survival information can be obtained via phone, and information will be documented in the source documents and appropriate eCRFs.

Information on all subsequent therapies received for NSCLC, if any, after study treatment has been completed, will be collected (including start date, stop date, and date of progression if any).

Post implementation of protocol amendment 05, survival follow-up will no longer be performed.

8.4 Safety

During treatment

Safety will be monitored by assessing physical examination, Eastern Cooperative Oncology Group (ECOG) Performance Status, vital signs, body weight, ECG, Patient Reported Outcomes, laboratory assessments, pregnancy tests, as well as collecting adverse events at every visit. For details on AE collection and reporting, refer to Section 10. Post implementation of protocol 05, performance status will no longer be performed. All safety assessments should be completed as per Table 8-2, Table 8-3 Table 8-4 and Table 8-5.

Post treatment discontinuation

All safety assessments (including pregnancy test for female subjects of child bearing potential) should be completed as per Table 8-2, Table 8-3, Table 8-4 and Table 8-5.

However, if the subject begins post-treatment antineoplastic medication before the completion of the 130-Day safety follow-up visit, only the new SAEs and AEs suspected to be related to study treatment will be collected up to the 130-Day safety follow-up visit.

After the 130-Day safety follow-up visit, only SAEs suspected to be related to study treatment will be collected during survival follow-up. Data collected should be added to the appropriate eCRF. Post implementation of protocol amendment 05, SAE experienced after the 130-day safety follow-up period should be reported to Novartis Safety only if the investigator suspects a causal relationship to the study treatment (Section 10.1.3).

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur as per the assessment schedule (or more frequently if needed) for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

8.4.1 Laboratory evaluations

Central safety laboratories will be used for the analysis of scheduled hematology, chemistry, and other blood specimens (Table 8-2 , Table 8-3 , and Table 8-8). The laboratory evaluations should be assessed on the actual scheduled day, even if study drug is being withheld. The time windows for laboratory evaluations correspond to the visit time windows for each visit (Table 8-1).

During the OLE phase, only local laboratory testing will be performed for safety evaluations (Table 8-4 and Table 8-7).

Post the implementation of protocol amendment 05, only local laboratory testing will be performed for safety evaluations aligned to standard of care with their current treatment and dosing regimen. (Table 8-5 and Table 8-8).

More frequent timepoints should be added as deemed necessary per the investigator's judgment to make sure toxicity profile is sufficiently characterized (e.g. DLT assessment in the safety run-in) and dose modifications performed to safeguard the safety of the subject. Additional results from unscheduled laboratory evaluations should be recorded on the appropriate eCRF.
Laboratory values obtained during the screening phase from the central laboratory will be used to assess eligibility. However, the site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made (e.g. confirmation of eligibility, study drug interruption, re-initiation, and/or termination). In those cases, local laboratory testing may be performed. The investigator is responsible for reviewing all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance. For visits with safety laboratory assessment only, a subject on-site visit may not be required, as per the investigator’s discretion, and local laboratory testing may be performed.
Dipstick urinalysis (macroscopic panel) will be performed at the site (unless local institution policies dictate otherwise), and in the case of any out of range parameters, a urine sample will be sent to central laboratory for further analysis (microscopic panel).
Details on the collection, sample shipment, and reporting of results by the central laboratory are provided in the Central Laboratory Manual and Flowchart.
If at any time a subject has laboratory parameters obtained from a local laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory. The results of the local laboratory will be recorded in the eCRF if any the following criteria are met:

- A treatment decision was made based on the local results, **or**
- There are no concomitant central results available, **or**
- Local lab results document an AE not reported by the central lab, **or**
- Local lab results document an AE where the severity is worse than the one reported by the central lab.

As per Section 4.6, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur as per the assessment schedule (or more frequently if needed) for safety monitoring and discussion of the subject´s health status until it is safe for the subject to visit the site again.

Table 8-7 Clinical laboratory parameters collection plan prior to implementation of protocol amendment 05

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells (RBC), White blood cells (WBC) with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils in percentage or absolute)
Chemistry	Albumin, ALT, AST, calcium[a] (at screening, calcium corrected for albumin will be tested in addition to calcium), creatinine, creatinine clearance[a], creatine kinase, total bilirubin, direct and indirect bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, fasting glucose[a], phosphate (inorganic phosphorus), alkaline phosphatase, amylase, pancreatic amylase (as needed), lipase, GGT
Thyroid	Total T3, FT4 and TSH
Coagulation	Pro-thrombin time (PT) and International normalized ratio [INR] or Quick Test
Hepatitis	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (baseline)
Infectious markers	Tuberculosis testing (as defined by country guidelines), HIV (where locally required)
Urinalysis	Macroscopic panel (Dipstick) (color, bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Pregnancy	At screening visit[a] and EOT, serum pregnancy test If local requirements dictate otherwise, local regulations should be followed
[a] not applicable for the OLE phase	

Table 8-8 Clinical laboratory parameters collection plan post implementation of protocol amendment 05

Test Category	Test Name
Hematology	Hemoglobin, Platelets, White blood cells (WBC) with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils in percentage or absolute)
Chemistry	Albumin, ALT, AST, creatinine, creatinine clearance, creatine kinase, total bilirubin, direct and indirect bilirubin (only if total bilirubin is ≥ grade 2)
Pregnancy	At EOT, serum pregnancy test If local requirements dictate otherwise, local regulations should be followed

8.4.1.1 Laboratory testings

Hematology, chemistry, thyroid function tests, coagulation, urinalysis and infectious disease marker tests are to be performed according to the visit schedule (Table 8-2 and Table 8-3). Laboratory assessment done ≤ 7 days of first dose of study treatment are permitted to be used as Cycle 1 Day 1 labs and do not need to be repeated

More frequent laboratory hematology testing may also be performed as medically necessary, and for accurate DLT determination in the safety run-in. Additional results from unscheduled hematology lab evaluations should be recorded on the appropriate electronic Case Report Form (eCRF).

Estimate of GFR (via estimated creatinine clearance rate) will be done using Cockcroft-Gault formula:

Estimated creatinine clearance rate (eC_{Cr}) using Cockcroft-Gault formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85\ if\ Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

When serum creatinine is measured in µmol/L:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

8.4.2 Determination of tuberculosis status

Determination of tuberculosis (active or latent) status will be required before administration of study drug and should be performed as defined by country guidelines. If presence of tuberculosis (active or latent) is established then treatment for tuberculosis must have been completed according to locally approved country guidelines prior to screening for the study. In case a subject develops tuberculosis during the study, this event must be followed-up and recorded in the eCRF.

8.4.3 Performance status

The performance status will be assessed according to the Eastern Cooperative Oncology Group (ECOG) performance status scale as specified in Table 8-9 (Oken et al 1982) following the schedule given in Table 8-2 , Table 8-3 and Table 8-4.

Post implementation of protocol amendment 05, performance status will no longer be performed.

Table 8-9 ECOG performance status

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

8.4.4 Electrocardiogram (ECG)

Local single 12-lead ECGs should be recorded prior to the dose administration, after the subject has been resting for 5-10 min prior to the timepoints indicated in Table 8-2,Table 8-3, Table 8-4 and Table 8-5.

An unscheduled ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Interpretation of the tracing must be made by a qualified physician and documented in the appropriate eCRF.

Each ECG tracing should be labeled with the study number, subject initials (where regulations permit), subject number, date, and kept in the source documents at the study site. Clinically significant ECG abnormalities present at screening should be reported on the appropriate eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded on the appropriate eCRF.

8.4.5 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed for all female subjects. Only for women of child bearing potential on Cycle 1 Day 1 prior to dosing and at subsequent cycles, a urine pregnancy test (dipstick) will be performed and a serum pregnancy test will also be completed at EOT. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit (Table 8-2 and Table 8-3). If local requirements dictate otherwise, local regulations should be followed.

During the OLE phase or post implementation of protocol amendment 05, only urine pregnancy test (dipstick) will be performed for women of child bearing potential, as shown on Table 8-4 and Table 8-5. Except at EOT, there will be a serum pregnancy test.

Women who are determined not to be of child bearing potential before the study will only complete a serum pregnancy test at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy), or bilateral tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential (such testing is not covered as part of the study assessments). If local requirements dictate otherwise, local regulations should be followed.

If a positive pregnancy test is obtained in between study visits, the subject must immediately notify the investigator. Male subjects must notify the investigator in case their partner becomes pregnant during the treatment period (Section 10.1.4).

As per Section 4.6, during a public health emergency as declared by local or regional authorities' i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if subjects cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant subjects can perform the urine pregnancy test at home and report the result to the site. It is important that subjects are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the subject so that the site is informed and can verify the pregnancy test results (e.g. following country specific measures).

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

The European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC-QLQ-C30), the lung cancer specific module (QLQ-LC13), and the EuroQoL 5-level instrument (EQ-5D-5L, tablet version) will be used to evaluate patient reported outcome (PRO) measures of health-related quality-of-life (QoL), physical functioning, disease symptoms, treatment-related side effects, global health status, and utilities (Aaronson et al 1993, Bergman et al 1994, Rabin and de Charro 2001).

All electronic PROs (ePROs) data will only be collected during the double-blind, randomized, placebo-controlled part of the study and in the OLE phase using an electronic tablet device provided by a CRO designated by Novartis. Subjects enrolled in the safety run-in part of the study will not complete ePROs. All ePRO assessments should be administered in the subject's local language according to the assessment schedule in Table 8-3 for the randomized part and Table 8-4 for the OLE phase, as applicable, prior to any assessments (including imaging assessments), treatments, or receipt of results from any test to avoid biasing the subject's perspective.

The ePROs will be completed prior to any other assessments on Day 1 of each cycle and at the End of Treatment visit (EOT) (Table 8-4), and then:

- For subjects who discontinue treatment due to RECIST 1.1 progression as per investigator and enter the safety follow-up period, ePROs will be collected within 7 days of the reported progression, and again at 28 days (-7 / +14 days) post progression.
- For subjects who discontinue study treatment for any reason other than RECIST 1.1 progression as per investigator and enter the efficacy follow-up period, ePROs will be collected at the same timepoints as the imaging assessments until RECIST 1.1 progression (on-site). Following progression, ePROs will then be collected within 7 days of the reported progression, and again at 28 days (-7 / +14 days) post progression.

During the OLE phase, ePROs will be completed following the same schedule as tumor assessments as well as at the EOT visit, during the efficacy follow-up and during the safety follow-up, as detailed above and in Table 8-4.

Subjects should be given sufficient space and time to complete all study questionnaires. If missing responses are noted, the tablet will alert subjects of any missing responses. Attempts should be made to collect complete questionnaires for all subjects.

The ePROs in this study are self-administered. If a subject is not able to self-administer the ePRO (e.g. due to illiteracy or blindness) or refuses to complete the questionnaires, this should be documented in the source documents and the questionnaires will not be completed. A subject's inability or refusal to complete study questionnaire(s) are not protocol deviations.

Please refer to the study ePRO manual for detailed instructions for completion and handling of the ePROs.

Post implementation of protocol amendment 05, the ePRO questionnaires will no longer be performed.

8.5.2 Pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamics (PD) assessments

To evaluate canakinumab exposure and immunogenicity in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of PK and anti-drug antibodies (ADA) are currently planned for canakinumab in the presence of pembrolizumab and various chemotherapy agents.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Samples are collected from the arm opposite from infusion site. If drug was administered via a central venous catheter, sample collection for PK (and IG/PD as applicable) should be from a different site. Timepoints of blood sample collection for canakinumab, pembrolizumab, and chemotherapy agents are outlined in Table 8-10 .

For all PK, IG, and PD analytes, the exact date and time of dosing, as well as the exact collection date and time of blood sampling must be recorded on the appropriate eCRF. All samples will be given a unique sample number and a dose reference ID.

If subjects experience an AE or SAE leading to a canakinumab dosing interval increase to Q6W or Q9W (see Section 6.5.3), do not collect canakinumab PK, PD, and/or IG samples on a visit cycle if canakinumab is not administered. Collect PK, PD, and/or IG samples if canakinumab is administered on a visit cycle in which samples are already scheduled as stated in protocol Table 8-10.

If subjects experience an AE or SAE leading to discontinuation of the study treatment, an unscheduled PK and IG blood sample should be obtained as close as possible to the event occurrence. If anaphylactoid reactions occur after injection, two more canakinumab IG samples (at the time of the event and 8 weeks later) need to be taken.

If dose level -1 (DL-1) of canakinumab 200 mg Q6W is explored as an alternative schedule, the canakinumab sampling scheme for Q6W regimen (also specified in Table 8-10) will be followed.

On days and time points where blood IG and PD samples are to be drawn, the PK sample must be drawn first.

During the OLE phase, there will be no PK, IG and PD sample collection done.

Refer to Central Laboratory Flowchart for detailed PK, IG and PD collection.

Post implementation of protocol amendment 05, the sample collection for analysis of PK, IG and PD will no longer be performed.

Table 8-10 Blood collection schedule for canakinumab (PK, IG and PD), pembrolizumab (PK and IG) and chemotherapy agents (PK)

Study Part	Analyte	PK/IG/PD	Scheduled time points for PK sampling*
Safety run-in (all subjects) Randomized (all subjects)	Canakinumab (Q3W)	PK	C1D1 pre-dose, C1D2, C1D8, C1D15; C2D1 pre-dose; C3D1 pre-dose; C4D1 pre-dose; C5D1 pre-dose, C5D8; C6D1 pre-dose; C8D1 pre-dose; C12D1 pre-dose; C16D1 pre-dose; EOT; safety follow up 26 days post EOT, safety follow up 78 days post EOT; safety follow up 130 days post EOT; Unscheduled
		IG	C1D1 pre-dose; C4D1 pre-dose; C8D1 pre-dose; C12D1 pre-dose; C16D1 pre-dose; EOT; safety follow up 26 days post EOT, safety follow up 78 days post EOT; safety follow up 130 days post EOT; Unscheduled
		PD (Total IL-1β)	C1D1 pre-dose, C1D15; C5D1 pre-dose; C16D1 pre-dose; EOT; safety follow up 26 days post EOT, safety follow up 78 days post EOT; safety follow up 130 days post EOT; Unscheduled
	Canakinumab (Q6W) (for dose level -1)	PK	C1D1 pre-dose, C1D2, C1D8, C1D15; C2D1; C3D1 pre-dose; C4D1; C5D1 pre-dose, C5D8; C7D1 pre-dose; C11D1 pre-dose; C15D1 pre-dose; EOT; safety follow up 26 days post EOT, safety follow up 78 days post EOT; safety follow up 130 days post EOT; Unscheduled
		IG	C1D1 pre-dose; C4D1; C7D1 pre-dose; C11D1 pre-dose; C15D1 pre-dose; EOT; safety follow up 26 days post EOT, safety follow up 78 days post EOT; safety follow up 130 days post EOT; Unscheduled
		PD (Total IL-1β)	C1D1 pre-dose, C1D15; C5D1 pre-dose; C15D1 pre-dose; EOT; safety follow up 26 days post EOT, safety follow up 78 days post EOT; safety follow up 130 days post EOT; Unscheduled
Safety run-in (all subjects) Randomized (subset of 60 subjects)	Pembrolizumab	PK	C1D1: pre-infusion, EOI (within 30 min), C1D2, C1D8, C1D15; C2D1 pre-infusion; C3D1 pre-infusion; C4D1 pre-infusion; C5D1 pre-infusion, EOI (within 30 min); C6D1 pre-infusion; C8D1 pre-infusion; C12D1 pre-infusion; C16D1 pre-infusion; EOT; safety follow up 26 days post EOT; Unscheduled
		IG	C1D1 pre-infusion; C2D1 pre-infusion, C4D1 pre-infusion; C8D1 pre-infusion; C12D1 pre-infusion; C16D1 pre-infusion; EOT; safety follow up 26 days post EOT; Unscheduled
Safety run-in (all subjects)	Pemetrexed	PK	C1D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 4 h (±10 min), 8 h (±10 min); C2D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 2 h (±10 min),4 h (±10 min), 8 h (±10 min); Unscheduled
Randomized (subset of 40 subjects)	Pemetrexed	PK	C1D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 4 h (±10 min); C2D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min); Unscheduled
Safety run-in (all subjects)	Cisplatin	PK	C1D1 pre-infusion, EOI (within 5 min), 2 h (±10 min), 4 h (±10 min), 8 h (±10 min); C2D1 pre-infusion, EOI (within 5 min), 1.5 h (±10 min), 2 h (±10 min),4 h (±10 min), 8 h (±10 min); Unscheduled
Randomized (subset of 40 subjects)	Cisplatin	PK	C1D1 pre-infusion, EOI (within 5 min), 2 h (±10 min), 4 h (±10 min); C2D1 pre-infusion, EOI (within 5 min), 1.5 h (±10 min), 2 h (±10 min), 4 h (±10 min); Unscheduled

Study Part	Analyte	PK/IG/PD	Scheduled time points for PK sampling*
Safety run-in (all subjects)	Carboplatin	PK	C1D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min), 8 h (±10 min); C2D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 2 h (±10 min),4 h (±10 min), 8 h (±10 min); Unscheduled
Randomized (subset of 40 subjects)	Carboplatin	PK	C1D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 2 h (±10 min), 4 h (±10 min)**; C2D1 pre-infusion, EOI (within 5 min), 1 h (±10 min), 2 h (±10 min),4 h (±10 min)**; Unscheduled **For paclitaxel + carboplatin regimen only, allow +/- 1 hr window for the 4 hour carboplatin collection.
Safety run-in (all subjects)	Paclitaxel	PK	C1D1 pre-infusion, EOI (within 5 min), 4 h (±10 min), 8 h (±10 min), 12 h (±10 min); C2D1 pre-infusion, EOI (within 5 min), 4 h (±10 min), 6 h (±10 min), 8 h (±10 min), 12 h (±10 min); Unscheduled
Randomized (subset of 25 subjects)	Paclitaxel	PK	C1D1 pre-infusion, EOI (within 5 min), 4 h (±10 min); C1D2 24 h (±1 h); C2D1 pre-infusion, EOI (within 5 min), 4 h (±10 min), 6 h (±1 h); C2D2 24 h (±1 h); Unscheduled
Randomized (subset of 25 subjects)	Nab-paclitaxel	PK	C1D1 pre-infusion, EOI (within 5 min), 4 h (±10 min), C1D2 24h (± 1 h); C2D1 pre-infusion, EOI (within 5 min), 4 h (±10 min), 6 h (±1 h);; C2D2 24 h (± 1 h); Unscheduled
EOI= end of infusion; EOT=end of treatment; *The collection time points are relative to s.c. canakinumab injection or beginning of i.v. infusion of respective drugs.			

8.5.2.1 Analytical method

Bioanalysis for PK, IG and PD assessments will employ the validated assays:

1. Canakinumab will be quantified in serum using a validated competitive enzyme-linked immunosorbent assay (ELISA) method, with an anticipated lower limit of quantification (LLOQ) of 100 ng/mL. The detailed method description to assess canakinumab (ACZ885) concentration will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).
2. The IG against canakinumab will be assessed in serum using a validated Meso Scale Discovery (MSD) electrochemiluminescence assay. The detailed method description to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective BDR.
3. An ELISA method will be used for bioanalytical analysis of total IL-1 Beta in serum, with an anticipated LLOQ of 0.299 ng/mL. The detailed method description to assess PD concentration will be described in the bioanalytical raw data of the study and in the respective BDR.
4. Pembrolizumab will be quantified in serum using a validated Ligand binding assay. Details of the method will be provided in the Bioanalytical data report (BDR).
5. The anti-drug antibodies (ADAs) against pembrolizumab will be assessed in serum using a validated immunoassay assay Details of the method will be provided in the bioanalytical data report (BDR).
6. Chemotherapy agents (paclitaxel, nab-paclitaxel, pemetrexed, carboplatin, and cisplatin) will be quantified in plasma using validated LC/MS and/or ICP-MS assays. The detailed

method will be described in the bioanalytical raw data of the study and in the respective BDR.

8.5.3 Biomarkers

The exploratory biomarker analysis will investigate whether the immune status of the tumor and its microenvironment are associated with the anti-tumor activity of canakinumab. The analysis will be performed in tumor biopsy samples collected at baseline, on treatment and time of progression, and using non-invasive samples taken at baseline, on treatment and post-treatment.

Blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Samples are collected from the arm opposite from infusion site. If the study treatment was administered via central venous catheter, sample collection for biomarkers should be from a different site. Refer to Central Laboratory Flowchart for details of mandatory and optional biomarker assessments.

For China only: biomarker tests will not be done unless approval has been obtained by all relevant Chinese authorities.

Post implementation of protocol amendment 05, the sample collection for analysis of biomarkers will no longer be performed.

8.5.3.1 Exploratory biomarker assessments in tumor biopsy samples collected at baseline, on-treatment and/or at progression

Mandatory tumor samples are to be collected at screening and may include resection, core, excisional and incisional biopsies. Fine needle aspirates are not acceptable sample types. Assessments may include but are not limited to immunohistochemistry (IHC) immune markers, immunological cells and related markers, gene expression profiling, sequencing of specific genes and determination of mutation load. Further, the on-treatment and progressive disease biopsies will be compared to baseline tumor to assess how the treatments affect the immune response at the level of the tumor.

8.5.3.2 Exploratory biomarker assessments performed using non-invasive samples

Assessments in blood samples collected at baseline, on treatment, post-treatment follow-up phase and at disease progression will include hs-CRP, hs-IL-6 and other cytokines and soluble protein biomarkers. The sequencing of specific gene panels and determination of mutation load using circulating DNA (ctDNA) will also be performed. Circulating tumor cells (CTCs) will be collected at baseline in a subset of subjects (approximately 60 subjects) to enable assessment of correlation between the PD-L1 levels in CTC versus tumor biopsy. Correlation between CTC counts and treatment outcome will also be evaluated.

Biomarker results (including hs-CRP) will be blinded and will not be communicated to the investigational sites during study conduct.

8.5.3.3 Additional biomarker assessments

Pharmacogenetic analysis

For subjects who sign the Optional Pharmacogenetic Patient Information and Informed Consent Form, one whole blood (sample will be collected, and used for assessments to identify predictive genetic markers. Additional retrospective pharmacogenetic analysis may be performed as well.

8.5.3.4 Use of residual biological samples

Optional additional biomarker studies

If the subject agrees, the biomarker samples that remain after analysis is completed (tumor, blood, plasma, and serum) may be kept for up to 15 years to be used for additional studies related to canakinumab or cancer, including research to help develop ways to detect, monitor or treat cancer. A decision to perform such exploratory biomarker research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

9 Discontinuation of study treatment and participant discontinuation/withdrawal

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is permanently stopped (prior to the planned completion of study treatment administration if any) , and can be initiated by either the subject or the investigator. The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Any situation in which continued study participation might result in a safety risk
- Unsatisfactory therapeutic effect
- Subject’s condition no longer requires study treatment
- Disease progression per RECIST 1.1 if it occurs when canakinumab/matching placebo is administered as a single agent
- Disease progression per RECIST 1.1 if it occurs when pembrolizumab was previously discontinued.

If discontinuation of study treatment occurs due to participant’s decision, the investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation of study treatment and record this information.

The investigator must contact the IRT to register the subject's discontinuation from study treatment. If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of assigned treatment code section (Section 6.6.2).

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (Section 9.2.2). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

For subjects who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent/opposition to use data/biological samples, tumor assessments must continue to be performed every 12 weeks until documented disease progression (per Investigator), death, lost to follow-up, or discontinuation from study or withdrawal of consent/opposition to use data/biological samples.

In some circumstances, subjects may be allowed to continue to receive study treatment beyond disease progression as per RECIST 1.1 criteria (Section 6.1.4.1). These subjects will continue assessment as outlined in Section 8 and will complete the end of treatment (EOT) visit only after permanent discontinuation of study treatment.

All subjects will have an EOT visit once all drugs of the study treatment are permanently discontinued (canakinumab, pembrolizumab, platinum-based doublet chemotherapy, and pemetrexed as applicable). Subjects should be scheduled for an EOT visit as soon as possible following the discontinuation of study treatment, at which time all assessments listed for EOT visit will be performed (Table 8-2, Table 8-3, Table 8-4 or Table 8-5). This visit should take place ≤ 7 days after the last dose of study treatment, if possible and appropriate eCRF page should be completed at this time, giving the date and reason for stopping the study treatment. EOT is not considered as end of study.

After study treatment discontinuation, all enrolled/randomized and/or treated subjects will be followed for AEs and SAEs for at least 130 days following the last dose of study treatment at the end of the treatment phase. Subjects will complete a total of five safety follow-up visits every 26 days until 130 days after the last dose of study treatment (Table 8-2, Table 8-3, Table 8-4 and Table 8-5). The information collected is kept in source documentation and in eCRF. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the subject should be recorded in the source documentation.

9.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 8 Visit schedule and assessments.

9.2.1.1 Replacement policy

Safety run-in part

Subjects will not be replaced on study. However, if a subject is considered as non-evaluable for the Dose-Determination Set (DDS), a new subject will be enrolled until at least the minimum number of 6 evaluable subjects is achieved within each treatment cohort.

Double-blind, randomized, placebo-controlled part

Subjects will not be replaced.

9.2.2 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation. Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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 subject are not allowed unless safety findings require communicating or follow-up. If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 8 Visit Schedule and assessments. Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding informed consent form.

9.2.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other subjects' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time. Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to subject s enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of investigational drug development in this indication.

In taking the decision to terminate, Novartis will always consider the subject welfare and safety.

Should early termination be necessary, subjects must be seen as soon as possible and treated as a subjects who discontinued from study treatment' (Section 9.1.1). 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 subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.3 Study completion and post-study treatment

The final PFS analysis and the 1st interim OS analysis in the randomized part will occur when approximately 253 PFS events are reached (Section 12.4), expected to occur approximately 18 months after the first subject randomized. At this time, a primary PFS/OS clinical study report (CSR) will be produced in case PFS or OS results are found statistically significant. The final analysis of the data from the safety run-in part will also be included in this primary PFS/OS CSR (Section 12).

After the primary PFS/OS CSR (if PFS alone is statistically significant), the study will remain open for the next OS analyses. Ongoing subjects will continue to receive study treatment and be followed as per the schedule of assessments (Table 8-2 and Table 8-3).

The primary OS analysis will take place when OS reaches statistical significance at either one of the interim or final OS analyses and the primary OS CSR will be produced. At this time the investigational sites will be unblinded for treatment allocation and subjects will transition to the OLE phase (Section 3). If OS is not statistically significant at final analysis but PFS was statistically significant at primary analysis, OLE will be initiated after final OS analysis, following the unblinding of investigational sites.

The study will end when all subjects discontinue the study treatment and complete their safety follow up, die, withdraw consent or are lost to follow up, whichever comes first. All available data from all subjects up to the final analysis cut-off date will be analyzed and summarized in

a final CSR. Also, in the event of an early study termination decision (Section 9.1.4), the end of the study is the date of that decision.

At the end of the study, every effort will be made in alignment with local regulations to continue provision of investigational treatment (canakinumab) or any of the other drugs (pembrolizumab and chemotherapy drugs as applicable) outside this study through an alternative setting to subjects who have not yet progressed per RECIST 1.1 as per investigator or iRECIST for subjects who in the opinion of investigator are still deriving clinical benefit.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any occurrence of unfavorable and unintended sign(s) [including abnormal laboratory findings], symptom(s) or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded in the eCRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0)
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.

4. Whether it constitutes a SAE (Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Outcome (not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the eCRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the eCRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Adverse events that begin or worsen after informed consent should be recorded in the eCRF. Conditions that were already present at the time of informed consent should be recorded in the eCRF. Adverse event monitoring should be continued for at least 130 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate adverse event.

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event, except if the investigator considers that progression of malignancy is related to study treatment.

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.

Information about adverse drug reactions for the investigational drug can be found in the Investigator Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- They induce clinical signs or symptoms
- They are considered clinically significant
- They require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from

baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease.

10.1.1.1 Adverse events of special interest

Adverse events of special interest (AESI) are defined as events (serious or non-serious) which are ones of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Adverse events of special interest are defined on the basis of an ongoing review of the safety data.

AESI for canakinumab include:

- Infections/Opportunistic infections
- Neutropenia
- Abnormal Liver Parameters
- Thrombocytopenia
- Immunogenicity/allergenicity
- Autoimmunity reactions
- Second primary malignancy
- Interactions with vaccines
- Interactions with drugs eliminated by CYP450 enzymes
- Pulmonary complications: pulmonary hypertension and interstitial lung disease
- Injection site reactions

Details regarding these adverse events are provided in the [canakinumab Investigator's Brochure]. Potential emergent new AEs will be monitored during the course of the study.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- Fatal
- Life-threatening - **Note:** Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - 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 subject's general condition
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- Is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Confirmed COVID-19 infection should be considered as medically significant and should therefore be reported as a SAE.

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until at least 130 days after the subject has stopped study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper backup within 24 hours of learning of its occurrence and until:

- At least 130 days following the last dose of study treatment **OR**
- The start of a new post study treatment antineoplastic medication if sooner than the 130 days mentioned above.

Note: Any SAEs experienced after the 130-day safety follow-up period and prior to start of new post study treatment antineoplastic medication should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Post implementation of protocol amendment 05, SAE experienced after the 130-day safety follow-up period should be

reported to Novartis Safety only if the investigator suspects a causal relationship to the study treatment. Please refer to Section 16.6 for safety follow-up diagram.

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

The following SAE reporting timeframes apply:

1. Screen Failures (e.g. a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.
2. Randomized OR Treated Subjects: SAEs collected between time subject signs ICF until 130 days after the subject has discontinued or stopped study treatment

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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 study treatment, a Novartis Safety 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 study treatment 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 EU Clinical Trial Regulation (EU-CTR) 536/2014 (if submitted under EU CTR) or EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

If a female subject becomes pregnant, the study treatment should be stopped, and the subject must be asked to read and sign the pregnancy consent form to allow the investigator to ask about her pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to Novartis Safety . Pregnancy follow-up should be recorded on the same form and should include an assessment of the

possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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.

If a pregnancy occurs while on study treatment, the newborn will be followed for up to 12 months.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the appropriate eCRF page irrespective of whether or not associated with an adverse event / serious adverse event (AE/SAE) and reported to safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in dose administration eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Data Monitoring Committee

This study will include a data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. The DMC will be constituted prior to the randomization of the first subject in part 2. The DMC will review at defined intervals the safety data as well as the efficacy and safety data from the final PFS analysis and interim OS analyses of the double-blind, randomized, placebo-controlled part of the study. The DMC meeting will be held approximately once per year. Additional DMC reviews may be performed if considered

appropriate by DMC. DMC will recommend to the sponsor whether to continue, modify or terminate a trial. Additional details on the conduct of final PFS and interim OS analyses can be found in Section 12.7

Specific details regarding composition, responsibilities, data monitoring and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate DMC charter that is established between the sponsor and the DMC.

10.2.2 Steering Committee

The steering committee (SC) will be established comprising investigators participating in the trial, i.e. not being members of the DMC and Novartis/sponsor representatives from the Clinical Trial Team.

The SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

11 Data Collection and Database management

11.1 Data collection

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 Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site. Data collected by third parties (imaging, safety lab, biomarkers, PK/IG/PD and PROs) will be sent electronically to Novartis. All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Data protection

Subjects will be assigned a unique identifier by Novartis. Any subject records or datasets that are transferred to Novartis will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

11.3 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff members 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 World Health Organization (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.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate (at time of the primary OS analysis), it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

DNA samples: The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the subject's medical records.

11.4 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and 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 subject 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 on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Part 1: Safety run-in part

The primary analysis of part 1 to determine the recommended phase 3 dose regimen (RP3R) will be conducted when at least 6 evaluable subjects in each of the 3 treatment cohorts have been observed for dose limiting toxicity (DLT) for the first 42 days (2 cycles) at the starting dose level to establish the RP3R. The final analysis of study data for Part 1 (safety run-in) will be conducted at the time of the primary analysis for Part 2 (randomized part), when approximately 253 PFS events are expected to have occurred in part 2. Data for all patients from part 1 are included.

Part 2: Double-blind, randomized, placebo-controlled part

The final PFS analysis in the double-blind, randomized, placebo-controlled part of the study will be performed after observing approximately 253 PFS events, in the full analysis set. The final OS analysis will be performed after observing approximately 304 deaths in the full analysis set (FAS) or at an earlier timepoint if OS meets statistical significance at one of the planned interim analysis.

Any additional data for ongoing subjects in the randomized part following the primary OS analysis and data for subjects in OLE (if initiated) will be further summarized in a final study report.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

12.1.1 Full Analysis Set

Part 1: Safety run-in part

The full analysis set (FAS) and safety set are defined in the same way and comprise all subjects to whom study treatment has been assigned and who received at least one dose of the study treatment (i.e. at least one dose of any component of the study treatment that is canakinumab or

pembrolizumab or platinum-based doublet chemotherapy (including incomplete infusion) or pemetrexed). Subjects will be analyzed according to the dose regimen they have been assigned to.

Part 2: Double-blind, randomized, placebo-controlled part

The FAS comprises of all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according to the treatment and strata which they have been assigned during the randomization procedure.

12.1.2 Safety set

Part 1: Safety run-in part

See definition of FAS.

Part 2: Double-blind, randomized, placebo-controlled part

The safety set includes all subjects who received at least one dose of any component of the study treatment. Subjects will be analyzed according to the study treatment they received, either canakinumab plus pembrolizumab plus platinum-based doublet chemotherapy or canakinumab matching-placebo plus pembrolizumab plus platinum-based doublet chemotherapy. The treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment (i.e. at least one dose of canakinumab or canakinumab matching-placebo) or the first treatment received if the randomized treatment was never received.

12.1.3 Dose-determining set

Part 1: Safety run-in part

The Dose-Determining Set (DDS) includes all subjects from the safety set who meet the minimum exposure criterion and have sufficient safety evaluations, or experienced a dose limiting toxicity (DLT) during the first 42 days (6 weeks) of dosing (definition of DLT refer to Section 6.5.2).

A subject meets the minimum exposure criterion if the subject received:

- At least 2 doses of canakinumab (for Q3W dosing regimen cohort) or at least 1 dose of canakinumab (for Q6W dosing regimen cohort in case the canakinumab dose is de-escalated to Q6W) and 2 infusions of pembrolizumab (full dose)
- Takes at least 75% of planned doses of the overall platinum-based doublet chemotherapy within the first 42 days (6 weeks) of study treatment

If the subject didn't receive these planned number of doses due to DLT, the subject will be considered meeting the minimum exposure criterion.

Subjects who do not experience a DLT during the first 42 days (6 weeks) are considered to have sufficient safety evaluations if they have been observed for ≥ 42 days (6 weeks) following the first dose, and are considered by the dose level review team (DLRT) to have sufficient safety data to conclude that a DLT did not occur.

Part 2: Double-blind, randomized, placebo-controlled part

Not applicable.

12.1.4 Pharmacokinetic set

Part 1: Safety run-in part

The Pharmacokinetic Analysis Set (PAS) consists of all subjects who received at least one dose of study drug and have at least one evaluable pharmacokinetic (PK) sample. The definition of an evaluable PK blood sample will be further specified in the statistical analysis plan (SAP). PAS will be defined for canakinumab, pembrolizumab, carboplatin, cisplatin, paclitaxel, and pemetrexed separately.

Part 2: Double-blind, randomized, placebo-controlled part

The PAS consists of all subjects who received at least one dose of study drug and have at least one evaluable PK sample. The definition of an evaluable PK blood sample will be further specified in the SAP. PAS will be defined for canakinumab, pembrolizumab, carboplatin, cisplatin, paclitaxel, nab-paclitaxel, and pemetrexed separately.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by canakinumab dose regimen and cohort for the FAS in the safety run-in part and by treatment group using the FAS and safety set for the double-blind randomized part. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

Relevant medical histories and current medical conditions at baseline will be summarized for the FAS by system organ class and preferred term, by canakinumab dose regimen and cohort in the safety run-in part and by treatment group for the FAS in the double-blind randomized part.

12.3 Treatments

The safety set will be used for the analyses below. The exposure related analyses will be presented by canakinumab dose regimen and treatment cohort for the safety run-in part and by treatment group for the double-blind randomized part.

The duration of exposure for study treatment and for each study drug (canakinumab, pembrolizumab, platinum-based doublet chemotherapy drugs and pemetrexed) will be presented. The dose intensity and the relative dose intensity will be summarized for each study drug component by descriptive statistics. The number of administrations (or treatment cycles) of each study drug component of the study treatment will be summarized by frequencies and descriptive statistics.

The number of subjects with dose adjustments (reductions, dosing interval increase, interruption, or permanent discontinuation) and the reasons will be summarized for each study drug. All dosing data will be listed.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system.

12.4 Analysis of the primary endpoint(s)

Part 1: Safety run-in part

The primary objective is to determine the recommended phase 3 dose regimen (RP3R) of canakinumab in combination with pembrolizumab, pemetrexed and carboplatin (cohort A) in non-squamous NSCLC cohort, canakinumab in combination with pembrolizumab, pemetrexed and cisplatin (cohort B) in non-squamous NSCLC cohort and canakinumab in combination with pembrolizumab, carboplatin and paclitaxel in squamous or non-squamous NSCLC cohort (cohort C).

Part 2: Double-blind, randomized, placebo-controlled part

The primary objectives of the study are to compare progression-free survival (PFS) by local investigator assessment as per RECIST1.1 and overall survival (OS) between the two study treatment arms.

12.4.1 Definition of primary endpoint(s)

Part 1: Safety run-in part

The primary endpoint is the incidence of dose limiting toxicities (DLT) in the first 42 days (6 weeks) of the study treatment. Refer to Section 6.5.2 for definition of DLTs.

Part 2: Double-blind, randomized, placebo-controlled part

The primary endpoints are PFS and OS endpoints:

- PFS is defined as the time from the date of randomization to the date of the first documented disease progression based on local investigator assessment as per RECIST 1.1 or death due to any cause
- OS is defined as the time from the date of randomization to the date of death due to any cause

Censoring conventions for PFS and OS are provided below in Section 12.4.3.

12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Safety run-in part (part 1)

Identification of recommended regimen

Determination of the RP3R will be based upon the estimation of the probability of DLT for the first 42 days (6 weeks) following the first dose for subjects in the dose-determining set (DDS). A lower recommended regimen may be identified based on other safety and PK data from the current study (Section 6.5.1.2).

Bayesian adaptive approach

The determination of RP3R will be guided by a Bayesian analysis of DLT data for each cohort for the first 42 days (6 weeks) during which subjects receive the combination of canakinumab, pembrolizumab and platinum-based doublet chemotherapy. The relationship between dose and the probability of DLT is modeled using logistic regression. Details of the Bayesian logistic regression model (BLRM) are given in Section 16.3 .

The dose limiting toxicity (DLT) relationship of canakinumab in combination with pembrolizumab and platinum-based doublet chemotherapy is modeled by a BLRM for each dose regimen that comprises single agent toxicity parts and interaction part. Single agent toxicity is modeled using logistic regression for the probability of a subject experiencing a DLT against log-dose. The odds of a DLT for each dose regimen are then calculated under no interaction for the single agent toxicities, and interaction is accounted for by adjusting these odds with additional model parameter (odds multipliers).

Starting dose

The starting dosing regimen are the following (Section 6.5.1.1):

- Cohort A: canakinumab 200 mg Q3W in combination with pembrolizumab 200 mg, carboplatin AUC 5 mg/mL*min and pemetrexed 500 mg/m^2 Q3W
- Cohort B: canakinumab 200 mg Q3W in combination with pembrolizumab 200 mg, cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 Q3W
- Cohort C: canakinumab 200 mg Q3W in combination with pembrolizumab 200 mg, carboplatin AUC 6 mg/mL*min and paclitaxel 200 mg/m^2 Q3W.

For this starting dose level of canakinumab (i.e. 200 mg Q3W), the prior risk of excessive toxicity (i.e. risk of DLT within [33%-100%]) is 15%, 10% and 22% for cohorts A, B and C, respectively, which satisfies the EWOC criterion.

Dose recommendation

Dose recommendations will be based on summaries of the posterior distribution of DLT rates for each dose level of the respective combination therapy. After each cohort of subjects, the posterior distribution for the risk of DLT for new subjects at combination doses of interest will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT for each dose regimen lies within the following intervals:

- Under-dosing: [0, 16%]
- Targeted toxicity: [16%, 33%]
- Excessive toxicity: [33%, 100%]

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

Listing of DLTs

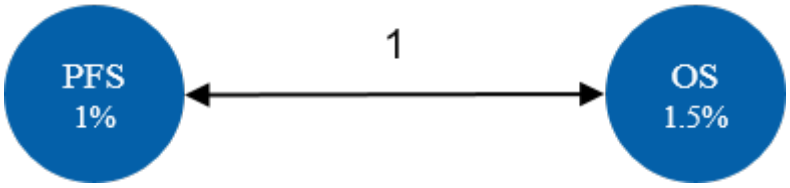
DLTs will be listed, and their incidence summarized by primary system organ class, preferred term and worst grade (CTCAE v5.0). Listings and summaries will be based on the DDS.

12.4.2.2 Double-blind, randomized, placebo-controlled part (Part 2)

12.4.2.2.1 Gate-keeping procedure

In order to conserve the overall type-1 error (one-sided level of significance α=0.025) in testing the primary endpoints of PFS and OS, an alpha split with a graphical gate-keeping approach will be implemented as shown in the figure below (Bretz et al 2009, Bretz et al 2011).

Figure 12-1 Graphical gate-keeping procedure to test primary endpoints in order to control overall type 1 error



12.4.2.2.2 Progression free survival (PFS)

Assuming a proportional hazards model for PFS, the null hypothesis will be tested at one-sided 1% level of significance. If OS is statistically significant at either interim or final analysis, then the 1.5 % alpha assigned to OS will be transferred to PFS and PFS will be tested at one-sided 2.5% level of significance.

H01 (null hypothesis): $\Theta 1 \geq 0$ vs. Ha1 (alternative hypothesis): $\Theta 1 < 0$

Where Θ1 is the log hazard ratio of PFS in the investigational arm vs. control arm.

In the primary analysis, PFS will be tested using the log-rank test stratified by randomization stratification factors when approximately 253 PFS events are observed. The statistical basis for a claim of efficacy will be the statistical significance (at the 1% one-sided level of significance if OS is not statistically significant at interim and final analysis or 2.5% one-sided level of significance if OS is statistically significant at either interim or final analysis) for PFS in favor of the canakinumab arm.

The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS and PFS rate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arms. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI based on the Wald test.

12.4.2.2.3 Overall survival (OS)

Assuming a proportional hazards model for OS, the null hypothesis will be tested at one-sided 1.5% level of significance. If PFS by investigator assessment per RECIST1.1 is statistically significant at 1% level of significance, then the 1 % alpha assigned to PFS will be transferred to OS and OS will be tested at one-sided 2.5% level of significance.

H_{02} (null hypothesis): $\Theta_2 \geq 0$ vs. H_{a2} (alternative hypothesis): $\Theta_2 < 0$

Where Θ_2 is the log hazard ratio of OS in the investigational arm vs. control arm.

In the primary analysis, OS will be tested using the log-rank test stratified by randomization stratification factors. The statistical basis for a claim of efficacy will be the statistical significance (at the 1.5% one-sided level of significance if PFS is not statistically significant at 1% one-sided level of significance or 2.5% one-sided level of significance if PFS is statistically significant at 1% one-sided level of significance) for OS in favor of the canakinumab arm.

The distribution of OS will be estimated using the Kaplan-Meier method. The median OS and OS rate at different timepoints along with 95% confidence intervals (CIs) will be presented by treatment arms. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of OS, along with 95% CI based on the Wald test.

12.4.3 Handling of missing values/censoring/discontinuations

Part 1: Safety run-in part

Subjects who are ineligible for the DDS will be excluded from the primary analysis (assessment of RP3R using incidence of DLT during first 42 days of treatment with canakinumab either in combination with pembrolizumab, carboplatin and pemetrexed or in combination with pembrolizumab, cisplatin and pemetrexed or in combination with pembrolizumab, carboplatin and paclitaxel), although their data will be used for all remaining analyses.

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

Part 2: Double-blind, randomized, placebo-controlled part

A subject whose disease has not progressed or died by the date of the analysis cut-off will have their PFS censored at the time of the last adequate tumor evaluation performed on or before the cut-off date. Clinical deterioration will not be considered as documented disease progression. Censoring rules for PFS follow the RECIST 1.1 guidelines and will be further detailed in the SAP.

A subject who has not died by the date of the analysis cut-off date will have their OS censored at the last known date the subject is alive.

12.4.4 Sensitivity and Supportive analyses

Part 1: Safety run-in part

Not applicable

Part 2: Double-blind, randomized, placebo-controlled part

Censoring summaries

The number of subjects censored for PFS and OS analysis and reasons for censoring will be summarized by treatment group.

PFS by BIRC assessment

As a supportive analysis of the primary endpoint of PFS by local investigator assessment, PFS by blinded review independent committee (BIRC) assessment will be analyzed using the same analytical conventions as the primary analysis. PFS assessed by BIRC will serve as supportive evidence of the primary endpoint. A sample based BIRC audit strategy will be used to assess PFS by BIRC based on the data from FAS.

Two methods that will be used to summarize the data from the sample-based BIRC assessment include:

- The ***NCI (National Cancer Institute) method*** (Dodd et al 2011) uses an auxiliary variable estimator of the log-hazard ratio that combines information from subject-level investigator assessment from all subjects and the BIRC assessment of these subjects randomly selected for central review. This estimate and its one-sided 95% CI will be provided. The NCI method will be used for audit sample size determination and summary of treatment effect (HR, 95% confidence intervals) based on the supportive BIRC assessment.
- The data from the BIRC assessment generated following the sampling scheme as above will also be summarized using the method proposed by Amit et al (2011), referred to as the ***PhRMA (Pharmaceutical Research and Manufacturers in America) method***. The differential discordance (DD) of the early discrepancy rate (EDR) and late discrepancy rate (LDR) between the treatment arms will be estimated using this approach. The EDR and LDR results will also be summarized by treatment arm.

Details of the audit sample size calculation for the BIRC assessment are provided in Section 12.8 .

Subgroup analyses for PFS and OS

If the primary endpoint analyses for PFS and/or OS are statistically significant, subgroup analyses to assess the homogeneity of the treatment effect across demographic and baseline disease characteristics will be performed for the subgroups as shown below.

The subgroups are:

- Gender (male vs. female)
- Age (<65 vs. ≥65 years)
- ECOG performance status (0 vs. 1)
- Smoking history (Former/Current vs. Never)
- PD-L1 baseline expression level (<1% vs. ≥1%, <50% vs. ≥50%, <1% vs. 1-49% vs. ≥50%, in case of non-evaluable PD-L1 status the subjects will be excluded from the subgroup analyses)
- Histology (squamous vs. non-squamous)
- Geographic region (East Asia vs. Western Europe and North America vs. Rest of the world)
- Chemotherapy regimen (pemetrexed+cisplatin vs. pemetrexed+carboplatin vs. carboplatin+paclitaxel vs. carboplatin+nab-paclitaxel)

- Tumor mutation burden (TMB) status at baseline (<10 mutations/megabase vs. ≥10 mutations/megabase, <16 mutations/megabase vs. ≥16 mutations/megabase)
- hs-CRP at baseline (<2mg/L vs. ≥2mg/L, <10mg/L vs. ≥10mg/L, <50 mg/L vs. ≥50 mg/L)

Additional subgroup analyses with different thresholds or variables (e.g. hs-CRP on treatment) may be conducted for PFS and OS. Details will be specified in the SAP .Sensitivity analyses will also be performed for OS and PFS in the FAS. Hazard ratio and 95% confidence interval for OS and PFS will be obtained from:

- an unstratified and covariate unadjusted Cox model.
- a stratified and covariate adjusted Cox model including covariates such as gender, age and smoking history.

The final list of covariates to be included in the model will be provided in the SAP. Additional sensitivity analyses will be detailed in the SAP.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

Part 1: Safety run-in part

In order to assess preliminary anti-tumor activity, overall response rate (ORR), disease control rate (DCR), and duration of response (DOR) will be summarized in FAS by dose regimen and cohort, using the local investigator assessment per RECIST1.1. For definitions of these endpoints, refer to Part 2 in Section 12.5.1 .

Part 2: Double-blind, randomized, placebo-controlled part

The secondary efficacy endpoints will be assessed using the FAS. The following analyses will be performed based on local investigator assessment:

ORR is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR), as per local review. ORR will be evaluated according to RECIST 1.1 (Section 16.1). CR and PR must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met. ORR will be estimated and the exact binomial 95% CI will be reported by treatment arm.

BOR for each subject is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR).
- SD = at least one SD assessment (or better) > 5 weeks after randomization (and not qualifying for CR or PR).
- PD = progression ≤ 13 weeks after randomization (and not qualifying for CR, PR or SD).

Disease control rate (DCR) is defined as the proportion of subjects with BOR of CR, PR, or stable disease (SD). DCR will be analyzed using the same analytical conventions as ORR.

Duration of response (DOR) is defined as the duration of time between the date of first documented response (CR or PR) and the date of first documented progression or death due to any cause. If a subject has not had an event, DOR is censored at the date of last adequate tumor assessment. Subjects who never achieved a BOR of CR or PR will be excluded from the analysis. The distribution function of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment arm.

Time to response (TTR) is defined as the time from the date of randomization to the date of first documented response (CR or PR, which must be confirmed subsequently). Subjects who did not achieve a confirmed CR or PR will be censored at the last adequate tumor assessment date when they did not have a PFS event or at maximum follow-up (i.e. FPFV to LPLV used for the analysis) when they did have a PFS event. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CIs will be presented by treatment arm.

ORR, DCR, DOR and TTR will be analyzed based on the data from FAS per RECIST1.1 based on local investigator assessment.

12.5.2 Safety endpoints

For the safety run-in part (Part 1), summary tables and listings will be presented by canakinumab dose regimen and cohort using the safety set. For the double-blind, randomized, placebo-controlled (Part 2), all listings and tables will be presented by treatment group using the safety set.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

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

1. Pre-treatment period: from day of subject's informed consent to the day before first dose of any component of the study treatment
2. On-treatment period: from day of first dose of any component of the study treatment to 130 days after last dose of any component of the study treatment
3. Post-treatment period: starting at day 131 after last dose of any component of the study treatment.

12.5.2.1 Adverse events

Summary tables for adverse events (AEs) will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and/or preferred term, severity (based on CTCAE v5.0) and relationship to study treatment.

Serious adverse events, non-serious adverse events and adverse events of special interest (AESI) during the on-treatment period will be tabulated. AESIs will be defined based on the case retrieval strategy (CRS) available at the time of the analysis.

All deaths (on-treatment and post-treatment) will be summarized overall and separately.

All AEs, deaths and serious adverse events (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period will be flagged.

12.5.2.2 Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per CTCAE v5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE 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 v5.0, results will be categorized as low/normal/high based on laboratory normal ranges.

The following summaries/listings will be generated separately for hematology, and biochemistry tests:

- Listing of all laboratory data with values flagged to show the corresponding CTCAE v5.0 grades if applicable and the classifications relative to the laboratory normal ranges

For laboratory tests where grades are defined by CTCAE v5.0

- Worst post-baseline CTCAE grade (regardless of the baseline status). Each subject will be counted only once for the worst grade observed post-baseline.
- Shift tables using CTCAE v5.0 grades to compare baseline to the worst on-treatment value

For laboratory tests where grades are not defined by CTCAE v5.0,

- Shift tables using the low/normal/high/ (low and high) classification to compare baseline to the worst on-treatment value.

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

12.5.2.3 Other safety evaluations

Vital signs

Data on vital signs will be tabulated and listed by treatment group, visit/cycle, notable values will be flagged. Summary statistics will be provided by treatment group.

Immunogenicity

Immunogenicity of canakinumab and pembrolizumab will be characterized descriptively by tabulating anti-drug antibodies (ADA) prevalence at baseline and ADA incidence on-treatment.

The impact of immunogenicity on PK, safety and efficacy may be explored and further details will be specified in the SAP.

12.5.3 Pharmacokinetics

The Pharmacokinetic Analysis Set (PAS) will be used in the pharmacokinetic data analysis in both safety run-in and randomized parts of the study. Descriptive statistics (n, m (number of non-zero concentrations), mean, coefficient of variation CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for canakinumab, pembrolizumab and chemotherapy agents separately will be presented at each scheduled timepoint for both safety run-in and double-blind, randomized, placebo-controlled parts of the study.

All concentration data for canakinumab, pembrolizumab and chemotherapy agents vs. time profiles will be displayed graphically.

The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented for PK parameters as well, except Tmax, where only n, median, minimum and maximum will be presented for canakinumab, pembrolizumab and chemotherapy agents, when applicable. PK parameters (e.g. AUC, Cmin, Cmax, Tmax, T1/2) will be estimated and reported at appropriate timepoints, when derivation of selective PK parameters is feasible.

12.5.3.1 Population pharmacokinetic analysis

If there is adequate amount of data, a mixed-effects model may be applied to the serum canakinumab concentration-time data from this study along with other studies to generate post-hoc estimates of pharmacokinetic parameters using NONMEM to characterize canakinumab exposure and to determine the effects of intrinsic (i.e. demographic factors) and extrinsic covariates (e.g. combination partners) on canakinumab exposure. If there is sufficient data for analysis, the details of the population pharmacokinetic analyses may be provided in a separate reporting and analysis plan, and the results may be reported in a separate population pharmacokinetic report. Similarly, population PK analysis may also be applied to pembrolizumab and chemotherapy agents to determine the effects of canakinumab on these agents.

12.5.3.2 Data handling principle

12.5.4 Patient reported outcomes

Three patient-reported outcomes (PRO) questionnaires will be assessed in the study part 2 only (double-blind, randomized, placebo-controlled part): EORTC QLQ-C30 with the lung cancer module QLQ-LC13 and the EQ-5D-5L.

QLQ-C30 and QLQ-LC13 will be considered as the primary scale. Scoring of PRO data and methods for handling of missing items or missing assessments will be handled according to the scoring manual and user guide for each respective subject questionnaire (Fayers 2001, VanReenen 2017). No imputation procedures will be applied for missing items or missing assessments.

The FAS will be used for analyzing PRO data. Analyses will include comparison of time to definitive 10-point deterioration between the 2 treatment arms using the EORTC QLQ-C30 with its lung cancer module QLQ-LC13. Time to definitive 10-point deterioration symptom scores for chest pain, cough and dyspnea per QLQ-LC13 questionnaire are the three primary PRO variables of interest. Utilities derived from EQ-5D-5L together with time to definitive deterioration in global health status/QoL, shortness of breath and pain per QLQ-C30 are the secondary PRO variables of interest. The time to definitive 10-point deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10 points absolute increase from baseline (worsening) of the corresponding scale score, with no later change below this threshold (i.e. <10 points was observed or if this increase was observed at the last assessment for the subject) or death due to any cause. If a subject has not had an event, time to definitive deterioration will be censored at the date of the last adequate assessment. It will be summarized using Kaplan-Meier curves. Summary statistics from Kaplan-Meier distributions will be determined, including the median time to definitive 10-point deterioration along with two-sided 95% confidence interval. Additionally, time to definitive deterioration with different cut-offs definition for deterioration may be specified in the SAP as deemed appropriate. A stratified Cox regression will be used to estimate the hazard ratio (HR), along with two-sided 95% confidence interval.

Descriptive statistics will be used to summarize the original scores, as well as change from baseline, of the QLQ-C30/QLQ-LC13 and EQ-5D-5L at each scheduled assessment timepoint for each treatment group. Additionally, change from baseline in the scale and subscale values at the time of each assessment will be summarized. Subjects with an evaluable baseline score and at least one evaluable post baseline score during the treatment period will be included in the change from baseline analyses.

The number of subjects completing each questionnaire and the number of missing or incomplete assessments will be summarized by treatment group for each scheduled assessment timepoint. No formal statistical tests will be performed for PRO data and hence no multiplicity adjustment will be applied.

In addition, a repeated measurement analysis model for longitudinal data will be used to estimate differences in EORTC QLQ-C30/QLQ-LC13 domains as well as the VAS and utility scores of the EQ-5D-5L between treatment arms. The differences in least square means between the treatment arms and corresponding 95% confidence interval at selected timepoints will be presented. Details, including handling of missing data, will be specified in the SAP.

12.6 Analysis of exploratory endpoints

12.6.1 Exploratory efficacy endpoints

Analysis of exploratory efficacy endpoints of iPFS, iORR, and iDCR based on local investigator assessment per iRECIST and PFS2 will also be performed. Analysis of all exploratory efficacy endpoints will be performed by treatment arm using the FAS and only on the double-blind, randomized, placebo-controlled part of the study.

Immune related progression-free survival (iPFS) is defined as the time from the date of randomization to the date of progression or death due to any cause. A progression event is defined as confirmed progression (iCPD), where the date of progression will be the date of first

iUPD assessment that was confirmed. In the absence of a confirmed progression, an unconfirmed progression (iUPD) with no further adequate tumor assessments will also be regarded as a progression event. If a subject has not had an event, progression-free survival will be censored at the date of last adequate tumor assessment. The iPFS distribution will be estimated using the Kaplan-Meier method, and the Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for iPFS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Immune related overall response rate (iORR) is defined as the proportion of subjects with a best overall response of iCR or iPR. iORR and its 95% confidence interval will be presented by treatment group.

Immune related disease control rate (iDCR) is defined as the proportion of subjects with best overall response of iCR or iPR or iSD. iDCR and its 95% confidence interval will be presented by treatment group.

PFS2: PFS2 is defined as time from date of randomization to the first documented progression on next line therapy or death from any cause, whichever occurs first. The PFS2 distribution will be estimated using the Kaplan-Meier method for each treatment arm. The hazard ratio for PFS2 will be calculated, along with its 95% confidence interval, using a Cox model stratified by randomization stratification factors. PFS2 will be performed using data from FAS.

12.6.2 Pharmacokinetics and pharmacodynamics (PK/PD) relationships

Descriptive statistics (n, m (number of non-zero concentrations), mean, CV%, SD, median, geometric mean, geometric CV%, minimum and maximum) for total IL-1β concentrations for valid PK samples will be presented at each scheduled timepoint. Concentration of total IL-1β vs. time profiles will be displayed graphically. A valid PK sample will be defined in the SAP.

The relationship between canakinumab PK, PD (inflammatory biomarkers such as hs-CRP and hs-IL-6), safety and efficacy (PFS, OS) may be explored and further details will be specified in the SAP.

12.6.3 Biomarkers

The statistical goals of exploratory biomarker analyses should be considered as promoting the generation of new scientific hypotheses and are exploratory in nature.

12.6.3.1 Outline of the data analysis

12.6.3.2 Data analysis principle

12.6.3.2.1 Analysis sets

FAS will be used for biomarker related analyses unless otherwise specified.

12.6.3.2.2 Basic tables, figures and listings

Depending on the endpoint of interest, graphical displays such as box plots or strip plots may be used to assess the relationship of different biomarkers with clinical benefit by treatment.

These may be separated by treatment arm and include either baseline or change from baseline values, where applicable.

For hs-CRP and hs-IL-6, baseline and change from baseline (absolute change, percent change and fold change) at each timepoint will be summarized in tables that include sample size, mean, standard deviation, %CV, median, minimum and maximum. For fold change from baseline, geometric mean and geometric %CV will also be included.

For categorical markers such as mutation status, 2x2 contingency tables may be used to assess the relationship with clinical benefit and/or Kaplan – Meier curves may be generated given the number of events warrant such an assessment.

If additional analyses are needed to be performed after the completion of the end-of-study clinical study report (CSR), they will be documented in separate reports. The data analysis will be described in an addendum of the statistical analysis plan (SAP) or in a stand-alone analysis plan document, as appropriate.

12.7 Interim analyses

Part 1: safety run-in part

The decision RP3R in the safety run-in will be based on analyses performed after each cohort in each chemotherapy regimen. More precisely, after each cohort of subjects the next dose will be chosen depending on the observed data (based on safety, PK, tolerability data, 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 6.5.1.2 .

Part 2: Double-blind, randomized, placebo-controlled part

There is no interim analysis (IA) for PFS. The final PFS analysis, is planned after approximately 253 PFS events have been observed. This is expected to occur approximately 18 months after the date of first subject randomized in part 2. The 1st IA for OS will be performed at the same time of final PFS analysis when approximately 120 over the 304 targeted OS events (39%) deaths are expected to be observed. The intent of this analysis is to assess superior efficacy with either PFS and/or OS results. There is no intent to assess futility at the time of the 1st interim OS analysis.

A maximum of three analyses will be performed for OS. The type I error probability will be controlled by using a Lan-DeMets (O'Brien-Fleming) alpha spending function (Lan and DeMets 1983) at the 1.5% (if PFS was not statistically significant) or 2.5% (if PFS was statistically significant) overall level of significance.

Based on the choice of alpha-spending function described above and if the first interim OS analysis is performed exactly at 120 OS events, the efficacy boundary expressed on the p-value scale (or the Z-statistic scale) at the interim is calculated as:

- $p < 0.0001082$(or $Z = 3.699$) if OS is tested at one-sided 1.5% alpha level
- $p < 0.0003604$(or $Z = 3.382$) if OS is tested at one-sided 2.5% alpha level

The observed (i.e., nominal) p-value has to be less than the p-value scale efficacy boundary defined above (or equivalently the observed z-statistic has to be > Z-statistic scale boundary) to declare statistical significance at 1.5% one-sided alpha level or 2.5% one-sided alpha level.

If the study continues to the 2nd IA for OS, it will be performed when approximately 243 OS events have been documented. If exactly 120 OS events are observed at the 1st IA for OS, the study continued and exactly 243 events are obtained at the 2nd IA for OS, the observed p-value will have to be less than 0.006 (or equivalently Z-statistic has to be >2.485) to declare statistical significance at 1.5% one-sided alpha level, or will have to be less than 0.012 (or equivalently Z-statistic has to be >2.255) to declare statistical significance at 2.5% one-sided alpha level. The 2nd interim OS analysis is anticipated to take place approximately 30 months after the first subject is randomized.

Since the observed number of events at the interim analyses may not be exactly equal to the planned 120 OS events at first interim OS analysis (or 243 OS events at 2nd interim analysis), the efficacy boundaries will need to be re-calculated using the pre-specified α-spending functions and based on the actual number of observed events at the corresponding interim and the total number of targeted events to calculate the exact information fraction. The observed p-value (or Z-test statistic or HR estimate) at each interim analysis will then be compared against the re-calculated efficacy boundaries.

If the study continues to the final OS analysis, the final OS analysis will be performed when approximately 304 OS events have been documented. In practice, the final analysis will be based on the actual number of OS events documented at the cut-off date for the final OS analysis and the alpha already spent at the interim analyses. The boundary for the final analysis will be derived accordingly from the pre-specified α-spending function such that the overall significance level across all analyses is maintained at 0.015 or 0.025 (if PFS results are found statistically significant at 1% level). The final OS analysis is expected to occur approximately 38 months after the first subject is randomized.

The statistical properties of the group sequential design are summarized in Table 12-1 below.

Table 12-1 Simulated probabilities to stop for overall survival efficacy at final PFS analysis, interim or final OS analyses

Scenario	Look	# deaths	Simulated cumulative probabilities	Simulated incremental probabilities
			Stop for efficacy	Stop for efficacy
If OS is tested at one-sided alpha=0.015				
Under H_0 (HR=1)	Final PFS (1st interim OS)	120	0.02%	0.02%
	2nd interim OS	243	0.65%	0.63%
	Final OS	304	1.44%	0.80%
Under H_a (HR=0.69)	Final PFS (1st interim OS)	120	4.5%	4.5%
	2nd interim OS	243	65.0%	60.5%
	Final OS	304	84.6%	19.6%
If OS is tested at one-sided alpha=0.025				
Under H_0 (HR=1)	Final PFS (1st interim OS)	120	0.04%	0.04%

Scenario	Look	# deaths	Simulated cumulative probabilities	Simulated incremental probabilities
			Stop for efficacy	Stop for efficacy
	2nd interim OS	243	1.25%	1.21%
	Final OS	304	2.40%	1.15%
Under H_a (HR=0.69)	Final PFS (1st interim OS)	120	8.6%	8.6%
	2nd interim OS	243	72.9%	64.3%
	Final OS	304	89.0%	16.1%

Note: Simulation is performed in East 6.4 with number of simulations=30, 000 and simulation seed = 1234. Any unblinding than can occur following final PFS and interim OS analyses, is described in Section 6.4.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Part 1: Safety run-in part

No formal statistical power calculations to determine sample size were performed for this part of the study. In the case that the starting dose (canakinumab 200 mg s.c. Q3W) with the fixed dose combination of pembrolizumab plus cohort specific platinum-based doublet chemotherapy is confirmed to be safe and tolerated, the safety run-in part is expected to enroll approximately 9 subjects in each treatment cohort in order to have at least 6 evaluable subjects , so approximately 27 subjects enrolled in total. Otherwise, additional subjects are foreseen to be enrolled to assess additional cohorts at canakinumab dose level-1 Q6W.

Part 2: Double-blind, randomized, placebo-controlled part

The sample size of the study is based on the 2 primary endpoints PFS and OS. The hypotheses to be tested and details of the testing strategy are described in Section 12.4.2 .

Progression-free survival (PFS)

Based on KEYNOTE-189 study (Gandhi et al 2018), the median PFS for pembrolizumab in combination with platinum-based doublet chemotherapy followed by pembrolizumab maintenance treatment (control arm) in subjects with non-squamous NSCLC is approximately 9 months. Based on KEYNOTE-407 (Paz-Ares 2018), the median PFS for pembrolizumab in combination with taxane-based chemotherapy followed by pembrolizumab maintenance treatment (control arm) in subjects with squamous NSCLC is 6.4 months. Based on the assumption that 30% subjects in this current study (CACZ885U2301) will have squamous histology (Rittmeyer et al 2017, Hellmann et al 2018), the median PFS in the control arm for this study is expected to be approximately 8 months based on simulation. Under the assumption that the median PFS in the control arm is 8 months, it is expected that addition of canakinumab will result in a 37.5% reduction in the PFS hazard rate (corresponding to an increase in median PFS from 8 months to 12.8 months under the exponential model assumption). If the true HR=0.625 (under the alternative hypothesis), a total of approximately 253 PFS events are required to have 92% power at a one-sided 1% level of significance if OS is not significant or

96.2% power at 2.5% level of significance if OS is significant to reject the null hypothesis (HR=1) using a log-rank test. If the final PFS analysis is performed when the targeted 253 PFS events are observed, the observed hazard ratio will have to be <0.746 or <0.782 to declare statistical significance at a one-sided 1% alpha level or 2.5% alpha level, respectively. Assuming a recruitment period of approximately 15 months from the start of the double-blind, randomized, placebo-controlled part with an accrual rate of 10 subjects/months for first 2 months, 20 subjects/months from 2 to 4 months, 40 subjects/months from 4 to 6 months and 50 subjects/month thereafter, along with an assumed 10% dropout rate/year for PFS, approximately 600 subjects will need to be randomized to the two treatment arms in a 1:1 ratio. Given the above assumptions it is estimated that the events for the final PFS analysis will occur at approximately 18 months from the date of first subject randomized in the study.

Overall survival

Based on KEYNOTE-189 (Gandhi et al 2018) , the 12-month OS rate for the subjects with non-squamous NSCLC randomized in pembrolizumab in combination with platinum-based doublet chemotherapy followed by pembrolizumab maintenance treatment (control arm) is 69.2%. Assuming an exponential distribution, median OS is derived to be approximately 23 months. Based on KEYNOTE-407 (Paz-Ares 2018), the median OS for pembrolizumab in combination with taxane-based chemotherapy followed by pembrolizumab maintenance treatment (control arm) in subjects with squamous NSCLC at the time of the 2nd IA is 15.9 months (95% CI: 13.2, NE). This median estimate may be immature given the high censoring rate and only ~30% of subjects had events. Therefore, the 9-month OS rate of 73% estimated graphically from the Kaplan-Meier curve was used to derive the median OS for the control arm in squamous NSCLC, which is calculated to be approximately 20 months assuming an exponential distribution. Based on the assumption that 30% subjects in the current study (CACZ885U2301) will have squamous histology, the median OS in the control arm for this study is expected to be approximately 22 months based on simulation. Under the assumption that the median OS in the control arm is 22 months, it is assumed that addition of canakinumab will result in a 31% reduction in the OS hazard rate (corresponding to an increase in median OS from 22 months to 31.9 months under the exponential model assumption). If the true HR=0.69 (under the alternative hypothesis), a total of approximately 304 deaths are required to have 85% power at a one-sided 1.5% level of significance if PFS is not significant or 89.3% power at 2.5% level of significance if PFS is significant to reject the null hypothesis (HR=1) using a log-rank test. If the final OS analysis is performed when the targeted 304 OS events are observed after exactly 120 OS events and 243 OS events have been observed at 1st and 2nd interim analysis respectively, the observed hazard ratio will have to be <0.775 or <0.793 to declare statistical significance at one-sided 1.5% alpha level or 2.5% alpha level respectively. A 5% dropout rate/year for OS is assumed. The interim analyses for OS are planned at the time of final PFS analysis and when approximately 80% of deaths are observed (expected at approximately 30 months from the date of first subject randomized). Events required for the final OS analysis are expected at approximately 38 months from the date of first subject randomized in the study.

These calculations were performed using EAST 6.4.

Audit size for BIRC assessed PFS

The audit size of the sample-based BIRC assessment will be 40% of all randomized subjects based on the audit size calculation approach proposed by Dodd et al 2011, assuming investigator and BIRC assessments are similar and the estimated log of investigator-based HR is -0.47 (i.e. HR=0.625). The audit size of 40% will ensure that the upper bound of a one-sided 95% CI for BIRC-based log-hazard ratio has 91 % probability of being below 0 (i.e. HR<1) if the correlation between investigator assessment and BIRC assessment is 0.8 (the estimated correlation approximated based on data from the Novartis [CLDK378A2303] and [CLDK378A2301] studies in NSCLC)

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. 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 Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (***defined as last patient last visit***) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard

Operating Procedures (SOPs) as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an 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 and Health Authorities, where required, it cannot be implemented.

14.1 Protocol Amendments

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 prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis must be notified of this action and the IRB/IEC at the study site must be informed according to local regulations.

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16 Appendices

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

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Glossary

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

16.1.1 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 2000) and the revised RECIST 1.1 guidelines (Eisenhauer 2009).

The efficacy assessments described in Section 16.1.2 and the definition of best response in Section 16.1.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.1.3.2 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 16.1.4 of this guideline describes data handling and programming rules. This section is to be referred to in the SAP (Statistical Analysis Plan) to provide further details needed for programming.

16.1.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria by (Therasse 2000) and revised RECIST guidelines (version 1.1) by (Eisenhauer 2009).

16.1.2.1 Definitions

16.1.2.1.1 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 subjects without measurable disease, even if not expected as per eligibility criteria in this protocol, see Section 16.1.3.2.9

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 5 mm 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 subject, 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.

16.1.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the subject 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 subjects be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how subjects with just non-measurable disease at baseline (even if not expected as per eligibility criteria of this protocol) will be evaluated for response and also handled in the statistical analyses is given in Section 16.1.3.2.9.

16.1.2.2 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 subjects, 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 subject 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 major change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change from

conventional to spiral CT or vice versa will not constitute a major "change in method" for the purposes of response assessment. A change in methodology will result by default in a UNK overall lesion response assessment as per Novartis calculated response. 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 new disease is indicated by a positive PET scan but is not confirmed by CT (or some other conventional technique such as MRI) at the same assessment, then follow-up assessments by CT will be needed to determine if there is truly progression occurring at that site. In all cases PD will be the date of confirmation of new disease by CT (or some other conventional technique such as MRI) rather than the date of the positive PET scan. If there is a positive PET scan without any confirmed progression at that site by CT, then a PD cannot be assigned.
  - 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.
- **Physical exams**: Evaluation of lesions by physical examination is accepted when lesions are superficial, with at least 10mm size, and can be assessed using calipers.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions, unless pre-specified by the protocol. 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 subject 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.

16.1.2.3 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 eCRF (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 16.1.2.1.1
- **Nodal target:** See Section 16.1.2.1.1.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 on-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.

16.1.2.4 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 16-1) and non-target lesions (Table 16-2) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-3) as well as the presence or absence of new lesions.

16.1.2.4.1 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

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.

16.1.2.4.2 Determination of target lesion response

Table 16-1 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. In exceptional circumstances an UNK response due to change in method could be over-ruled by the investigator or central reviewer using expert judgment based on the available information (see Notes on target lesion response and methodology change in Section 16.1.2.2).

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 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 eCRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 16-1 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 subjects who have not achieved target response of CR. For subjects who have achieved CR, please refer to last bullet in this section.
- For those subjects 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.
- A change in method for the evaluation of one or more lesions will usually lead to an UNK target lesion response unless there is progression indicated by the remaining lesions which have been evaluated by the same method. In exceptional circumstances an investigator or central reviewer might over-rule this assignment to put a non-UNK response using expert judgment based on the available information. E.g. a change to a more sensitive method might indicate some tumor shrinkage of target lesions and definitely rule out progression in which case the investigator might assign an SD target lesion response; however, this should be done with caution and conservatively as the response categories have well defined criteria.

16.1.2.4.3 Determination of non-target lesion response

Table 16-2 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[2].

1. The assignment of PD solely based on change in non-target lesions in light of target lesion response of CR, PR or SD should be exceptional. In such circumstances, the opinion of the investigator or central reviewer prevails.
2. It is recommended that the investigator and/or central reviewer should use expert judgment to assign a Non-UNK response wherever possible (see notes section for more details)

Notes on non-target lesion response

- The investigator and/or central reviewer can use expert judgment to assign a non-UNK response wherever possible, even where lesions have not been fully assessed or a different method has been used. In many of these situations it may still be possible to identify equivocal progression (PD) or definitively rule this out (non-CR/Non-PD) based on the available information. In the specific case where a more sensitive method has been used indicating the absence of any non-target lesions, a CR response can also be assigned.
- 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 there is unequivocal progression of the non-target lesions (in which case response is PD) or it is not possible to determine whether there is unequivocal progression (in which case response is UNK).
- 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 16.1.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

16.1.2.4.4 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 eCRF 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 subject in which case the response should be UNK, as for any of this subject's assessment (Section 16.1.2.5).
- 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 16.1.2.2.

16.1.2.5 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 16-3.

Table 16-3 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 16.1.2.4.

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

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.

16.1.3 Efficacy definitions

The following definitions primarily relate to subjects who have measurable disease at baseline. Section 16.1.3.2.9 outlines the special considerations that need to be given to subjects with no measurable disease at baseline in order to apply the same concepts.

16.1.3.1 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 subject'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 130 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 subject 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) > 5 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression <=13 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 5 weeks or early progression within the first 13 weeks)

The time durations specified in the SD/PD/UNK definitions above are based on a 6 week tumor assessment frequency taking into account assessment windows. E.g. if the assessment occurs every 6 weeks with a time window of +/- 7 days, a BOR of SD would require a SD or better response longer than 5 weeks after randomization/start of treatment.

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A subject 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 subject 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 subject. 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 subject 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 subject 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 subjects' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of subjects 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 subjects with a best overall response of CR or PR or SD. The objective of this endpoint is to summarize subjects with signs of "activity" defined as either shrinkage of tumor (regardless of duration) or slowing down of tumor growth.

Clinical benefit rate (CBR) is the proportion of subjects with a best overall response of CR or PR , or an overall lesion response of SD or Non-CR/Non-PD which lasts for a minimum time duration (with a default of at least 24 weeks in breast cancer studies). This endpoint measures signs of activity taking into account duration of disease stabilization.

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 subjects with progressive disease within 7 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 subjects who at the specified assessment do not have an overall lesion response of SD, PR or CR. subjects 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, subjects 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).

16.1.3.2 Time to event variables

16.1.3.2.1 Progression-free survival

Usually in all Oncology studies, subjects 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 subject has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

PFS rate at x weeks is an additional measure used to quantify PFS endpoint. It is recommended that a Kaplan Meier estimate is used to assess this endpoint.

16.1.3.2.2 Overall survival

All subjects should be followed until death or until subject has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the subject was last seen alive / last known date subject 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 subject is not known to have died, survival will be censored at the date of last known date subject alive.

16.1.3.2.3 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 subject has not had an event, time to progression is censored at the date of last adequate tumor assessment.

16.1.3.2.4 PFS2

A recent EMA guidance 2012 recommends a substitute end point intermediate to PFS and OS called PFS2, a surrogate for OS when OS cannot be measured reliably, which assesses the impact of the experimental therapy on next-line treatment. The main purpose of this endpoint is to assess long term maintenance strategies, particularly of resensitizing agents and where it is necessary to examine the overall "field of influence".

PFS2, which could be termed PFS deferred, PFS delayed, tandem PFS, or PFS version 2.0, is the time from date of randomization/start of treatment to the date of event defined as the first documented progression on next-line treatment or death from any cause. The censoring rules for this endpoint will incorporate the same principles as those considered for PFS in this document, and in addition may involve other considerations which will need to be detailed in the protocol.

Please note that data collection for the PFS2 is limited to the date of progression and not specific read of the tumor assessments.

It is strongly recommended that the teams consult regulatory agencies for scientific advice given the limited experience with the use of this endpoint in regulatory setting in light of methodological issues w.r.t. censoring foreseen.

16.1.3.2.5 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 subjects who did not experience treatment failure will be censored at last adequate tumor assessment.

16.1.3.2.6 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 subjects: a good risk group and a poor risk group. Good risk subjects tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk subjects 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 subjects. Less potent agents induce a response mainly in good risk subjects only. This is described in more detail by (Morgan 1988).

It is recommended that an analysis of all subjects (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 subjects (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis 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-subject analysis of these endpoints are not appropriate since the status of subjects throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For subjects 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 subjects 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 subjects 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.

16.1.3.2.7 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 16.1.3.2.6. It is recommended that an analysis of all subjects (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 subjects should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all subjects, subjects 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 subjects 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 subject 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 subjects 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.

16.1.3.2.8 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.

In the calculation of the assessment date for time to event variables, any unscheduled assessment should be treated similarly to other evaluations.

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 16.1.3.2.8).

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 subject 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 subject 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.

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

It is possible that subjects with only non-measurable disease present at baseline are entered into the study, because of a protocol violation. 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 subjects 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 subjects with measurable disease at baseline, subjects without measurable disease should also be incorporated in an appropriate manner. The overall response for subjects with non-measurable disease is derived slightly differently according to Table 16-4.

Table 16-4 Overall lesion response at each assessment: subjects 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 16.1.2.4.		

In general, the **non-CR/non-PD response** for these subjects is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response subjects 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 subjects 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 subjects with only non-measurable disease at baseline, handling subjects with a best response of CR as "responders" with respect to ORR and all other subjects as "non-responders".

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

16.1.3.2.10 Sensitivity analysis

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 subject 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 16.1.3.2.8, and using the FDA guideline on endpoints (FDA Guidelines 2007) as a reference, the following analyses can be considered:

Table 16-5 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

Situation		Options for end-date (progression or censoring)1 **(1) = default unless specified differently in the protocol or RAP**	Outcome
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) Ignore clinical progression and follow situations above (2) Date of discontinuation (visit date at which clinical progression was determined)	As per above situations Progressed
F	New anticancer therapy given	(1) Ignore the new anticancer therapy and follow situations above (ITT approach) (2) Date of last adequate assessment prior to new anticancer therapy (3) Date of secondary anti-cancer therapy (4) Date of secondary anti-cancer therapy	As per above situations Censored Censored Event
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 16.1.3.2.8.

2 =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.1.3.2.8.

3 =The rare exception to this is if the subject 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 subjects 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) (ITT) is the recommended approach; events documented after the initiation of new cancer therapy will be considered for the primary analysis i.e. progressions and deaths documented after the initiation of new cancer therapy would be included as events. This will require continued follow-up for progression after the start of the new cancer therapy. In such cases, it is recommended that an additional sensitivity analysis be performed by censoring at last adequate assessment prior to initiation of new cancer therapy.

Option (2), i.e. censoring at last adequate assessment may be used as a sensitivity analysis. If a high censoring rate due to start of new cancer therapy is expected, a window of approximately 8 weeks performed after the start of new cancer therapy can be used to calculate the date of the event or censoring. This should be clearly specified in the analysis plan.

In some specific settings, local treatments (e.g. radiation/surgery) may not be considered as cancer therapies for assessment of event/censoring in PFS/TTP/DoR analysis. For example, palliative radiotherapy given in the trial for analgesic purposes or for lytic lesions at risk of fracture will not be considered as cancer therapy for the assessment of BOR and PFS analyses. The protocol should clearly state the local treatments which are not considered as antineoplastic therapies in the PFS/TTP/DoR analysis.

The protocol should state that tumor assessments will be performed every x weeks until radiological progression irrespective of initiation of new antineoplastic therapy. It is strongly recommended that a tumor assessment is performed before the subject is switched to a new cancer therapy.

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 16-5 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.

16.1.4 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).

16.1.4.1 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).

16.1.4.2 End of treatment phase completion

Subjects **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 subjects 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 subject, e.g., dates of telephone calls, registered letters, etc.

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

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

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

Death is a reason which "*must*" lead to discontinuation of subject from trial.

16.1.4.3 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.

Subjects 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
- Progressive disease
- Study terminated by the sponsor

16.1.4.4 Medical validation of programmed overall lesion response

In order to be as objective as possible the RECIST programmed calculated response assessment 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). This contrasts with the slightly more flexible guidance given to local investigators (and to the central reviewers) to use expert judgment in determining response in these type of situations, and therefore as a consequence discrepancies between the different sources of response assessment often arise. To ensure the quality of response assessments from the local site and/or the central reviewer, the responses may be re-evaluated by clinicians (based on local investigator data recorded in eCRF or based on central reviewer data entered in the database) 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 subjects with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

16.1.4.5 Programming rules

The following should be used for programming of efficacy results:

16.1.4.5.1 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.

16.1.4.5.2 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 16.1.3.2.8). 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.

16.1.4.5.3 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.

16.1.4.5.4 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)'.

16.1.4.5.5 Study / project specific programming

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

16.1.4.5.6 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 (optional, see Table 16-5)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

* Adequate assessment is defined in Section 16.1.3.2.8. 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 subjects 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.

16.1.5 References (available upon request)

Dent S, Zee B, Dancey J, et al (2001) application of a new multinomial phase II stopping rule using response and early progression. J Clin Oncol: 19:785-91.

Eisenhauer EA, Therasse P, BogaertsJ, et al (2009) New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Euro JCancer; 45:228-47.

Ellis S, Carroll KJ, Pemberton K, et al (2008) Analysis of duration of response in oncology trials. Contemp Clin Trials; 29:456-65.

EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal products in man

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18

Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors. J **Natl** Cancer Inst ;, 92; 205-16

16.2 Appendix 2: Guidelines for iRECIST

Changes from iRECIST Version 1.0:

The main purpose of the amendment is to incorporate the additional clarifications provided by iRECIST EORTC working group. Below are the key changes:

Clarified the conditions under which the overall response can be reset following unconfirmed progression (iUPD) in Section 16.2.2.4.4

- The target and non-target lesion response tables (Table 16-6 and Table 16-7) were simplified based on the reset of response criteria provided in Section 16.2.2.4.4
- The new lesion-target and new lesion-non-target response Section 16.2.2.4.3.1 and Section 16.2.2.4.3.2 were added to provide guidance on assessment of response based on new lesion- target and new lesion- non-target lesions. It is important to follow the existing new lesions as it can remain as iUPD due to no change in size, result in confirmation of progression (iCPD), disappear completely resulting in iCR or shrink in size resulting in a response of iSD
- Overall lesion response table (Table 16-10) was updated taking into account the new lesion-target and new lesion-non-target response
- Example scenarios in Section 16.2.5 were updated to include the target response, non-target response, new lesion-target response and new lesion-non-target response rows
- Scenario 4 was updated based on clarifications provided by iRECIST EORTC working group on confirmation of progression (iCPD) following missing assessments after iUPD

16.2.1 Introduction

This guideline provides the general principles and application of iRECIST (modified RECIST 1.1 for immune-based therapeutics) to assess tumor response and to derive efficacy endpoints in Novartis oncology immunotherapy clinical trials. This guideline is based on the publication: “iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics in solid tumors” by Seymour et al 2017.

This guideline will also refer to Novartis RECIST 1.1 (v3.2) for sections and derivations which are unchanged from RECIST 1.1.

This document is organized as follows:

- Section 16.2.2 describes the efficacy assessments: disease measurability, methods of tumor assessments, baseline documentation of target/non-target lesions, follow-up of target, non- target and new target/non-target lesions and evaluation of overall lesion response
- Section 16.2.3 provides the definitions and derivations of immune related best overall response and time to event endpoints
- Section 16.2.4 lists references used in the text
- Section 16.2.5 provides the example scenarios

16.2.2 Efficacy assessments

Tumor evaluations are done based on iRECIST criteria (Seymour et al 2017) and RECIST 1.1 guidelines (Eisenhauer et al 2009).

16.2.2.1 Disease measurability

The definition of disease measurability, classification of baseline lesions into target and non-target lesions, measurement and management of nodal disease, and calculation of sum of diameters (SOD) remains the same as RECIST 1.1. Please refer to Novartis RECIST 1.1 (v3.2) Section 16.1 for details.

While there is no requirement to measure new lesions in RECIST 1.1, the new lesions identified at follow-up evaluations will be assessed and categorized as target or non-target in iRECIST using the same criteria of measurability as in RECIST 1.1. For additional details on handling of new lesions in iRECIST refer to Section 16.2.2.3.3.

16.2.2.2 Methods of tumor measurement

The methods used to measure tumors remain the same as RECIST 1.1. Please refer to Novartis RECIST v3.2 Section 16.1 for details.

16.2.2.3 Target, non-target and new lesions

The methods used to classify lesions at baseline remains the same as RECIST 1.1. Please refer to Novartis RECIST 1.1 (v3.2) Section 16.1 for details.

16.2.2.3.1 Target lesions

The selection of target lesions at baseline and their follow-up with the calculation of baseline/follow-up sum of diameters (SOD) should be performed as per RECIST 1.1.

16.2.2.3.2 Non-target lesions

The selection of non-target lesions at baseline and their follow-up with the assessment of lesion status should be performed as per RECIST 1.1 with the exception of the follow-up evaluations following unconfirmed progression based on these non-target lesions. Please refer to Section 16.2.2.4.2 for further details.

16.2.2.3.3 New lesions

A lesion not present at baseline and appearing at any follow-up evaluation time-point (TP) is considered a New Lesion. A new lesion will be considered as ‘Newly appeared’ at a follow- up evaluation TP if it appeared for the first time at that TP and did not exist prior to that TP. For all subsequent TP, this new lesion will be not considered as ‘Newly appeared’ and will be followed as a “Pre-existing” new lesion.

New lesions appearing at a follow-up evaluation TP will be classified either as New Lesion Target (NLT) or New Lesion Non-Target (NLNT) based on the TP when they were first identified using the same measurability criteria mentioned in RECIST 1.1. Once a new lesion is classified as NLT or NLNT, it should be followed as NLT and NLNT respectively at each subsequent TP regardless of change in size. New lesions do not have to resolve for subsequent

overall response assessment of iSD or iPR provided the next assessment did not confirm progression (see Section 16.2.2.4.3).

New Lesions Target

All new measurable lesions up to a maximum of 5 new lesions (nodal + non-nodal) in total (and a maximum of 2 lesions per organ), representative of all involved organs should be identified as New Lesions Target (NLT). Each NLT should be uniquely and sequentially numbered, measured and recorded in the eCRF corresponding to "New Lesions Target". A sum of diameters (iSOD; long axis for non-nodal lesions, short axis for nodal) for all NLT will be calculated at each follow-up evaluation TP from the first appearance of a NLT. NLTs should not be included in the sum of diameter of the original target lesions identified at baseline.

New Lesions Non-target

All other new lesions which are not considered as new lesions-target at the corresponding evaluation TP will be considered as New Lesions Non-Target (NLNT). Multiple NLNTs involved in the same organ can be recorded as a single NLNT (i.e. multiple liver metastases). Each NLNT should be uniquely numbered in the appropriate eCRF. The lesion status of the NLNT at each follow-up evaluation compared to the "previous assessment" should be recorded at each follow-up evaluation TP.

16.2.2.4 Response evaluation

Response will be assessed using iRECIST based on Seymour et al 2017. Response assigned using iRECIST will have a prefix of an 'i' (i.e. immune) (e.g. iCR for complete response) to differentiate them from RECIST 1.1 response.

The principles used to establish objective tumor response are largely unchanged from RECIST 1.1. The major change in iRECIST is the concept of unconfirmed disease progression (iUPD) and confirmed disease progression (iCPD). The response evaluation will remain the same for RECIST 1.1 and iRECIST up to the first iUPD timepoint.

Following are the key differences in response evaluation based on iRECIST compared to RECIST 1.1:

- Confirmation of disease progression is required per iRECIST. This leads to two separate response categories for overall response corresponding to progressive disease: unconfirmed progressive disease (iUPD) and confirmed progressive disease (iCPD); the rules for confirmation of disease progression are provided in Section 16.2.2.4.4.
- New lesions are to be separately followed and measured at subsequent evaluation TPs in iRECIST for response assessment.
- An iUPD can be followed by a complete (iCR) or partial response (iPR) or stable disease (iSD) or Non-iCR/Non-iUPD (for subjects with only non-measurable disease at baseline, even if not expected as per eligibility criteria of this protocol) as overall response. If this happens, the bar (i.e. overall response) is "reset" and iUPD needs to re-occur per RECIST 1.1 followed by iCPD in order for the progression to be confirmed.

16.2.2.4.1 Target lesion response

The target lesion response will be assessed based on the criteria shown in Table 16-6.

Table 16-6 Determination of target lesion response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune Complete Response (iCR)	Any post-baseline evaluation TP prior to confirmation of progression (i.e. determination of overall lesion response of iCPD)	Same as CR criteria for target lesions by RECIST 1.1. iCR will be target lesion response at the next assessment if CR criteria per RECIST 1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune Partial Response (iPR)	Any post-baseline evaluation TP prior to confirmation of progression (i.e. determination of overall lesion response of iCPD)	Same as PR criteria for target lesions by RECIST 1.1 (i.e. reduction in target lesion SOD>=30% from baseline). iPR will be target lesion response at the next assessment if PR criteria per RECIST 1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune Stable Disease (iSD)	Any post-baseline evaluation TP prior to confirmation of progression (i.e. determination of overall lesion response of iCPD)	Same as SD criteria for target lesions by RECIST 1.1 (i.e. neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD) iSD will be target lesion response at the next assessment if SD criteria per RECIST 1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was not iUPD	Same as PD criteria for target lesions by RECIST 1.1 (i.e. increase in target lesion SOD ≥20% from nadir with an absolute increase of ≥5 mm). For iUPD after iCR, follow RECIST 1.1.
	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided the overall response is not reset and there is no confirmation of iUPD*. •
Not Evaluable (NE)	Any post-baseline evaluation TP	Same as UNK (Unknown)/NE (Not evaluable) criteria for target lesions by RECIST 1.1

*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.2.2.4.4.

For additional notes on target lesion response (e.g. reappearance of lesions, lesion split/coalesced etc.) refer to Novartis RECIST 1.1 (v3.2).

16.2.2.4.2 Non-target lesion response

The non-target lesion response will be assessed based on the criteria shown in Table 16-7 .

Table 16-7 Determination of non-target lesion response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune Complete Response (iCR)	Any post-baseline evaluation TP prior to confirmation of progression (i.e. determination of overall lesion response of iCPD)	Same as CR criteria for non-target lesions by RECIST 1.1 iCR will be non-target lesion response at the next assessment if CR criteria per RECIST1.1 is met and the overall response is reset after the previous assessment of overall response of iUPD*.
Immune Non-CR/non-UPD (Non-iCR/Non-iUPD)	Any post-baseline evaluation TP prior to confirmation of progression (i.e. determination of overall lesion response of iCPD)	Same as NON-CR/NON-PD criteria for non- target lesions by RECIST 1.1 Non-iCR/Non-iUPD will be non-target lesion response at the next assessment if the overall response is reset after the previous assessment of overall response of iUPD*.
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was not iUPD	Same as PD criteria for non-target lesions by RECIST 1.1 (i.e. unequivocal progression of non-target lesions). For iUPD after iCR follow RECIST 1.1.
	A post-baseline TP prior to iCPD where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided the overall response is not reset and there is no confirmation of iUPD*.
Not Evaluable (NE)	Any post-baseline evaluation TP	Same as UNK (Unknown)/NE (Not evaluable) criteria for non-target lesions by RECIST 1.1
*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.2.2.4.4		

For additional notes on non-target lesion response (e.g. unequivocal progression etc.) refer to Novartis RECIST 1.1 (v3.2).

16.2.2.4.3 New lesion consideration in response

As mentioned in Section 16.2.2.3.3, the new lesions are classified as New Lesions Target (NLT) and New Lesions Non-Target (NLNT). Both NLT and NLNT will contribute to the overall response determination; however, will not be added to the SOD for baseline target lesions.

- A NLT or NLNT appearing for the first time at any post-baseline evaluation TP will result in an overall lesion response of iUPD unless it confirms disease progression which occurred at the previous TP. If it confirms disease progression which occurred at the previous TP, then overall lesion response will be iCPD.
- Recurrence of iUPD after return to iSD or better response following previous iUPD will be based on RECIST 1.1 principles. The new lesions would result in a new iUPD if:
  - New lesion appeared at that TP.
  - The pre-existing NLT met RECIST 1.1 criteria for PD i.e. 20% or more increase in iSOD from nadir with an absolute increase of ≥ 5 mm. Nadir iSOD is obtained based on all previous TP assessments of NLT.
  - The pre-existing NLNT showed unequivocal worsening.
- New lesions do not have to resolve for a subsequent overall lesions response of iSD or iPR if there is a reset of overall response

16.2.2.4.3.1 New lesion-target (NLT) response

The new target lesion response will be applicable only from the time point of appearance of new target lesion(s) until the disappearance of the new target lesion(s). The new target lesion response will be assessed based on the criteria shown in Table 16-8.

Table 16-8 Determination of new lesion-target response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP from the appearance of new-target lesion and prior to iCPD, where the previous adequate evaluation TP overall response was not iUPD	A new target lesion appears at the current TP or pre-existing NLT met RECIST 1.1 PD criteria based on iSOD from new target lesions (At least 20% increase in iSOD relative to nadir or baseline with at least 5 mm absolute increase)
	A post-baseline TP from the appearance of new-target lesion and prior to iCPD, where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided there is no change in size of new target lesions and the overall response is not reset and there is no confirmation of iUPD*
Immune Stable Disease (iSD)	A post-baseline evaluation TP after the appearance of a new target lesion prior to iCPD	iSD will be new target lesion response at the next assessment following iUPD if there is change in size of new target lesions and the previous TP overall response of iUPD will be reset to iSD or better*
Immune Partial Response (iPR)	NA	
Immune Complete Response (iCR)	A post-baseline evaluation TP after the appearance of a new target lesion prior to iCPD	Disappearance of all new target lesions
Not Evaluable (NE)	A post-baseline evaluation TP after the appearance of a new target lesion	Same as UNK (Unknown)/NE (Not evaluable) criteria per RECIST 1.1
*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.2.2.4.4.		

16.2.2.4.3.2 New lesion-non-target response

The new non-target lesion response will be applicable only from the time point of appearance of new non-target lesion(s) until the disappearance of the new non-target lesion(s). The new non-target lesion response will be assessed based on the criteria shown in Table 16-9.

Table 16-9 Determination of new lesion-non-target response by iRECIST

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
Immune unconfirmed progressive disease (iUPD)	A post-baseline TP from the appearance of new non-target lesion and prior to iCPD. where the previous adequate evaluation TP overall response was not iUPD	A new non-target lesion appears at the current TP or pre-existing NLNT showed unequivocal worsening

Time point (TP) response criteria	Applicable to Evaluation Time-points	Evaluation criteria
	A post-baseline TP from the appearance of new non-target lesion and prior to iCPD, where the previous adequate evaluation TP overall response was iUPD	iUPD will remain iUPD provided there is no change in new non-target lesions and the overall response is not reset and there is no confirmation of iUPD*
Immune Non-CR/non-UPD (NON-iCR/NON-iUPD)	A post-baseline evaluation TP after the appearance of a new non-target lesion prior to iCPD	NON-iCR/NON-iUPD will be the new non-target lesion response if there is change in new non-target lesions and the previous overall response of iUPD will be reset to iSD or better*
Immune Complete Response (iCR)	A post-baseline evaluation TP after the appearance of a new non-target lesion prior to iCPD	Disappearance of all new non-target lesions
Not Evaluable (NE)	A post-baseline evaluation TP after appearance of a new non-target lesion	Same as UNK (Unknown)/NE (Not evaluable) criteria for non-target lesions by RECIST 1.1
*For details on confirmation of progression (iCPD) and the reset of overall response after prior iUPD refer to Section 16.2.2.4.4.		

16.2.2.4.4 Confirmation of disease progression and reset of overall lesion response

Unlike RECIST 1.1, iRECIST requires confirmation of progression. A confirmatory scan should be performed at least 4 weeks after initial iUPD and no longer than 8 weeks after iUPD, provided the subject is clinically stable and does not require change of treatment. If progression is confirmed at the confirmatory scan, the overall lesion response will be iCPD. If the next assessment after iUPD is not evaluable (NE), then the next adequate tumor assessment will be considered for the determination of iCPD.

Confirmation of progression requires either

- further worsening in the lesion category (i.e. target, non-target, new lesion) with existing iUPD

or

- a lesion category without prior iUPD met RECIST 1.1 criteria for progression.

Overall lesion response will be assessed as iCPD based on the following criteria if there is a further continued increase in tumor burden compared to the previous TP response of iUPD:

- If initial iUPD was due to Target lesions: further increase in target lesions of at least 5 mm* in the absolute value of SOD compared to the iUPD from previous TP.
- If initial iUPD was due to Non-Target lesions: Any increase in non-target lesions compared to the iUPD from previous TP.
- If initial iUPD was due to New lesions: Further increase in size of new lesion(s) (an increase of at least 5 mm* in iSOD of NLT or any increase in NLNT) compared to the iUPD from previous TP or appearance of additional new lesions at current TP.
- RECIST 1.1 criteria for PD was met in lesion categories (target or non-target or appearance of additional new lesions), where iUPD was not previously identified.

*Note: Sequential increases are additive; Thus a 4 mm increase at one assessment, followed at the next assessment by a further 2 mm increase meets the criteria for iCPD.

If progression (iUPD) was not confirmed at the next evaluation TP (i.e. no iCPD), then ; there are two scenarios for overall lesion response at the next evaluation TP as defined below:

- The overall lesion response is reset with response of iSD or better if it meets RECIST 1.1 criteria even if the new lesions do not resolve
- iUPD will remain at the next evaluation TP if there is no change in tumor burden or it meets PD per RECIST 1.1 criteria
    - No change in tumor burden is defined as <5mm change in SOD/iSOD based on target/new-target lesions and no change in the status of non-target/new non-target lesions.

The overall lesion response is reset with a TP response of iSD or better if it meets RECIST 1.1 criteria (even if the new lesions do not resolve), after the previous evaluation TP response of iUPD, if it meets one of the below criteria compared to the TP, where prior iUPD was observed:

- Decrease of at least 5 mm in SOD based on target lesions
- Shrinkage in non-target lesions resulting in reduction of tumor burden
- Decrease of at least 5 mm in iSOD based on new target lesions
- Shrinkage in new non-target lesions resulting in reduction of tumor burden

After the overall lesion response is reset following iUPD, the target, non-target, new lesion target and new lesion non-target response evaluation will follow the criteria specified in Table 16-6, Table 16-7, Table 16-8 and Table 16-9.

Note: Even if the overall lesion response is reset, all assessments including those assessments done prior to reset of response should be considered for determination of nadir, which will be used to determine the next occurrence of iUPD.

16.2.2.4.5 Overall lesion response

The overall lesion response for a post-baseline TP will be assessed as shown in Table 16-10.

Table 16-10 Overall lesion response for a time-point based on consideration of target lesions, non-target lesions and new lesions

Row #	Target lesion response*	Non-target lesion response*	New lesion response*		Overall TP response	
			Target†	Non-target††	No prior iUPD**	Prior iUPD**; ***
1	iCR	iCR	iCR	iCR	iCR	iCR
2	iCR	NON-iCR/NON-iUPD	iCR, iSD	iCR, NON-iCR/NON-iUPD	iPR	iPR
3	iPR	iCR, NON-iCR/NON-iUPD	iCR, iSD	iCR, NON-iCR/NON-iUPD	iPR	iPR as long as there is no iCPD
4	iSD	iCR, NON-iCR/NON-iUPD	iCR, iSD	iCR, NON-iCR/NON-iUPD	iSD	iSD as long as there is no iCPD
5	iUPD with no change or decrease from last TP	iUPD with no change or decrease from last TP	No iCPD due to new-target lesions	No iCPD due to new non-target lesions	NA	iUPD remains unless iCPD confirmed
6	iSD, iPR, iCR	iUPD	iUPD, iCR	iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed

Row #	Target lesion response*	Non-target lesion response*	New lesion response*		Overall TP response	
			Target†	Non-target††	No prior iUPD**	Prior iUPD**; ***
7	iUPD	NON-iCR/NON-iUPD or iCR	iUPD, iCR	iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
8	iUPD	iUPD	iUPD, iCR	iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
9	Non-iUPD	Non-iUPD	iUPD	iUPD, NON-iCR/NON-iUPD, iCR	iUPD	Remains iUPD unless iCPD confirmed
10	Non-iUPD	Non-iUPD	iUPD, iSD, iCR	iUPD	iUPD	Remains iUPD unless iCPD confirmed

* Using RECIST 1.1 principles.

If no RECIST PD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD will be the same.

** in any lesion category.

*** previously identified in assessment immediately prior to this TP. If this is not the case then refer to column 'No prior iUPD'.

† Only applicable on/after the time point a new lesion-target appeared. If there are no new lesions-target consider new lesion-target response as if it is iCR.

†† Only applicable on/after the time point a new lesion-non-target appeared. If there are no new lesions-non-target consider new lesion-non-target response as if it is iCR.

If there are no baseline scans available, then the overall response at each assessment will be Not Evaluable (NE).

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 iCR.

For subjects with only non-measurable disease at baseline (even if not expected as per eligibility criteria of this protocol), the overall response will be obtained based on Non-target response (refer to Table 16-7) and new lesions (Table 16-8, Table 16-9). Table 16-10 can be used for obtaining the overall response without considering the target lesion requirement in this situation.

16.2.2.5 Treatment continuation beyond RECIST 1.1 PD

Differentiating transient pseudo-progression from true progression, potentially requiring a change in therapy, can be challenging. Although early discontinuation of an effective drug is not desirable, continued long-term treatment with a non-effective drug past true progression might delay the initiation of potentially effective salvage therapy.

All decisions regarding continuation or discontinuation of therapy should be made by the investigator in conjunction with the subject. It is recommended that clinical trials, which permit treatment beyond initial RECIST 1.1 defined progression (i.e., iUPD) should only allow subjects who are clinically stable to continue on treatment until the next assessment (≥4 weeks later) and is still deriving benefit as per investigator assessment. The next imaging assessment after RECIST 1.1 PD should ideally be no longer than 8 weeks later, to ensure that subjects remain fit for salvage therapies. A longer timeframe before the next assessment may be

reasonable if pseudo-progression is well described in the tumor type, especially if no effective salvage therapies are available and this should be justified in the trial protocol.

The imaging findings and the recommendation to continue treatment despite iUPD should be discussed with the subject before a decision is made about whether or not to continue therapy. subjects who have iUPD and are not clinically stable should be designated as not clinically stable in the case report form and it is recommended that the treatment should be withdrawn. The determination of clinical stability/benefit which would allow continuation of therapy will need to be made at the initial progression based on RECIST1.1 PD (iUPD by iRECIST) and at each subsequent assessment of iUPD.

16.2.2.5.1 Guidance on assignment of clinical stability

An assignment of clinical stability generally requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.

16.2.3 Efficacy definitions

16.2.3.1 Best overall response

For best overall response (BOR), the requirement for confirmation of progression needs to be taken into account for the derivation but otherwise the same principles as described in the Novartis RECIST 1.1 (v3.2). Section 16.1.3.1 will apply unless stated otherwise below or in the study protocol.

The best overall response for each subject is determined from the sequence of overall responses recorded while on treatment or till start of new antineoplastic therapy according to the following rules:

- iCR = at least two determinations of iCR at least 4 weeks apart. Note that there should not be any tumor assessment with an overall response of iUPD in between.
- iPR = at least two determinations of iPR or better at least 4 weeks apart (and not qualifying for iCR). Note that there should not be any intervening tumor assessment with an overall response of iUPD in between.
- iSD = at least one iSD assessment (or better) > 5 weeks after randomization/start of treatment (and not qualifying for iCR or iPR).
- iCPD = iCPD with initial iUPD assessment of the progression ≤ 13 weeks after randomization/ start of treatment (and not qualifying for iCR, iPR or iSD) For example
  - If overall response for TP1= iUPD; TP2 = iUPD; TP3 = iUPD and TP4 = iCPD then iBOR = iCPD.
  - If overall response for TP1= NE; TP2 = iUPD; TP3 = iUPD and TP4 = iCPD then iBOR = iCPD.
- iUPD = iUPD with no further adequate tumor assessments ≤ 13 weeks after randomization/ start of treatment (and not qualifying for iCR, iPR, iSD or iCPD)

- NE = all other cases (i.e. not qualifying for confirmed iCR or iPR and without iSD after more than 5 weeks or early progression within the first 13 weeks)

The primary analysis of the best overall response will be based on the sequence of investigator (investigator overall lesion responses).

Additional Notes

- If the subject has a confirmed progression (iCPD) 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.

- Overall lesion responses of iCR (which may have to be a confirmed iCR depending on the study) must stay the same until an iUPD assessment, with the exception of an NE status. A subject who had a iCR, and confirmed (if required), cannot subsequently have a lower status other than an iUPD (or iCPD), e.g. iPR or iSD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become an iUPD.
- Similarly, once an overall lesion response of iPR is observed (which may have to be a confirmed iPR depending on the study) this assignment must stay the same or improve over time until an iUPD assessment, with the exception of a NE status.

For subjects with only non-measurable disease at baseline (even if not allowed in this protocol) no confirmation is required for Non-iCR/Non-iUPD. For the BOR, the same definition as above applies for iCR, iPD and NE. For BOR of Non-iCR/Non-iUPD the definition for iSD will be used.

16.2.3.2 Definition of endpoints

16.2.3.2.1 Frequency-based endpoints

Immune related overall response rate (iORR) is defined as the proportion of subjects with a best overall response of iCR or iPR. This is also referred to as 'immune-related objective response rate' in some protocols or publications.

Immune related complete response rate (iCRR) is defined as the proportion of subjects with a best overall response of iCR. (For studies with a reasonable number of responders expected)

Immune related disease control rate (iDCR) is defined as the proportion of subjects with a best overall response of iCR or iPR or iSD. Subjects with a BOR of iNCRNPD will also be included in iDCR if subjects with non-measurable disease at baseline are in the analysis set.

Immune related clinical benefit rate (iCBR) is defined as the proportion of subjects with a best overall response of iCR or iPR or overall lesion response of iSD or Non-iCR/Non-iPD lasting for at least 24 weeks.

16.2.3.2.2 Time to event endpoints

For the following time to event endpoints, a progression event will be defined as:-

- A confirmed progression (iCPD), where the date of progression will be the date of first iUPD assessment that was confirmed.

For example, if the sequence of overall lesion response at different TPs is as shown below:

Post-baseline TP	1	2	3	4	5	6
Overall response	iSD	iUPD	iPR	iUPD	iUPD	iCPD

The date of progression for analysis will be the date of TP4.

- In the absence of a confirmed progression, an unconfirmed progression (iUPD) with no further adequate tumor assessments will also be regarded as a progression event. In this case, the progression date will be the date of the first iUPD assessment with no intervening iSD or better overall response.

For example, if the sequence of overall lesion response at different TPs is as shown below:

Post-baseline TP	1	2	3	4	5	6
Overall response	iSD	iUPD	iPR	iUPD	iUPD	NE

The date of progression will be the date of TP4. TP2 is not considered since there is an intervening iPR at TP3.

Any unconfirmed progression assessments (iUPD) which are subsequently followed by at least one further adequate tumor assessment will be ignored in the derivation of these endpoints. An adequate tumor assessment is a tumor assessment with overall response other than NE. If the sequence of overall lesion response at different TPs is as shown below:

Post-baseline TP	1	2	3	4	5	6	7
Overall response	iSD	iUPD	iPR	iUPD	iUPD	iSD	NE

The above is not a progression event and it will be censored in the time to event analysis with the date of censoring at TP6.

1. **Immune related progression-free survival (iPFS)**

iPFS is defined as the time from date of randomization/start of treatment to the date of progression or death due to any cause. If a subject has not had an event, progression-free survival will be censored at the date of last adequate tumor assessment. iUPD without further adequate tumor assessments will be considered as an event. An adequate tumor assessment is a tumor assessment with overall response other than NE. Refer to Novartis RECIST 1.1 (v3.2) for additional details on censoring rules.

2. **Immune related time to progression (iTTP)**

iTTP is defined as the time from date of randomization/start of treatment to the date of progression or death due to underlying cancer. If a subject has not had an event, time to progression will be censored at the date of last adequate tumor assessment. iUPD without further adequate tumor assessments will be considered as an event. An adequate tumor assessment is a tumor assessment with overall response other than NE. Refer to Novartis RECIST 1.1 (v3.2) for additional details on censoring rules.

3. **Immune related time to response (iTTR)**

iTTR is defined as the time between date of randomization/start of treatment until first documented response (confirmed iCR or iPR). Time to response will be censored for subjects without confirmed iCR or iPR as described in the Novartis RECIST 1.1 (v3.2).

4. **Immune related duration of response**

Immune related duration of overall response (iDOR): For subjects with a confirmed iCR or iPR the start date will be the date of first documented confirmed response and the end date and censoring will be defined the same as that for time to progression (iTTP).

The following two durations may be calculated in addition for a large Phase III study in which a reasonable number of responders are observed.

Immune related duration of overall complete response: For subjects with a confirmed iCR the start date will be the date of first documented confirmed iCR and the end date and censoring will be defined the same as that for time to progression (iTTP).

Immune related duration of stable disease: For subjects with BOR of iCR (confirmed) or iPR (confirmed) or iSD the start and end date as well as censoring will be defined the same as that for time to progression (iTTP).

16.2.4 References

Eisenhauer EA, Therasse P, et al (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1), European Journal of Cancer; 45, p228-247.

Seymour L, Bogaerts J, Perrone A, et al (2017) iRECIST: guidelines for response criteria for use in trials testing immunotherpeutics, Lancet Oncol, 18, e143-52.

16.2.5 Supplement 1: Example Scenarios

Below are some example scenarios which are included for clarity on how the criteria can be used in specific situations.

16.2.5.1 Scenario 1: Cross category PD

	Baseline	**TP1**	**TP2**	**TP3**
TL (SOD mm)	100	125	125	125
NTL	Present	UC	UC	Unequi. ↑
NLT (# of NLT/ iSOD mm)	-	-	-	-
NLNT	-	-	-	-
TP response (RECIST)	-	PD	PD	PD
TL response (iRECIST)		iUPD	iUPD	iCPD
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	iUPD
NLT response (iRECIST)	-	-	-	-
NLNT response (iRECIST)	-	-	-	-

TP response (iRECIST)	-	iUPD	iUPD	iCPD
TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non-Target; TP = Time-point; UC = Unchanged				

- RECIST/iRECIST PD/iUPD at TP1 based on Target lesions
- iRECIST iUPD at TP2 due to no change in lesions.
- iRECIST Confirmed PD at TP3 due to non-target unequivocal progression which confirms the initial TP1 iUPD observed based on target lesions.
- iBOR will be iCPD. TP1 will be used as event date for iPFS/iTTP/iDOR.

16.2.5.2 Scenario 2: iPR after initial iUPD

	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
TL (SOD mm)	100	125	50	52	52	60
NTL	Present	UC	UC	UC	UC	UC
NLT (# of NLT/ iSOD mm)	-	-	-	-	+/11	+/11
NLNT	-	+	UC	UC	+	UC
TP response (RECIST)	-	PD	PD	PD	PD	PD
TL response (iRECIST)	-	iUPD	iPR	iPR	iPR	iUPD
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
NLT response (iRECIST)	-	-	-	-	iUPD	iUPD
NLNT response (iRECIST)	-	iUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
TP response (iRECIST)	-	iUPD	iPR	iPR	iUPD	iCPD
TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non-Target; TP = Time-point; UC = Unchanged; + denotes appearance of one new lesion						

- RECIST/iRECIST PD/iUPD at TP1 due to target lesions and new lesion
- iPR at TP2 as iUPD was not confirmed and target lesions met PR criteria per RECIST 1.1 even though NLNT remained unchanged. The status is reset with this iPR. Previous iUPD will no longer be considered.
- iPR at TP3 as target lesions met PR criteria per RECIST 1.1 even though NLNT remained unchanged.
- Recurrence of iUPD at TP4 based on another NLT.
- iCPD at TP5 because target lesions met PD criteria per RECIST 1.1 .
- iBOR will be iPR. TP4 will be used as event date for iPFS/iTTP/iDOR

16.2.5.3 Scenario 3: iPR before and after iUPD

	Baseline	TP1	TP2	TP3	TP4	TP5	TP6
TL (SOD mm)	100	60	70	70	65	55	55
NTL	Present	UC	UC	UC	UC	UC	UC
NLT (# of NLT/ iSOD mm)	-	-	-	+/ 10	+/ 12	+/ 12	+/ 18
NLNT	-	-	-	-	-	-	
TP response (RECIST)	-	PR	PR	PD	PD	PD	PD
TL response (iRECIST)	-	iPR	iPR	iPR	iPR	iPR	iPR
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
NLT response (iRECIST)	-	-	-	iUPD	iSD	iSD	iUPD
NLNT response (iRECIST)	-	-	-	-	-	-	-
TP response (iRECIST)	-	iPR	iPR	iUPD	iPR	iPR	iUPD

TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non-Target; TP = Time-point; UC = Unchanged;

+ denotes appearance of one new lesion

- RECIST/iRECIST PR/iPR at TP1 and TP2 due to >=30% decrease in target lesion SOD compared to baseline.
- RECIST/iRECIST PD/iUPD at TP3 due to a NLT of 10 mm.
- iRECIST iPR at TP4 as iUPD was not confirmed and PR was met based on RECIST 1.1 and there is improvement in target lesion compared to TP3 iUPD. NLT increased slightly but did not meet iCPD criteria. The status is reset with this iPR. Previous iUPD will no longer be considered.
- iRECIST iPR at TP5.
- iUPD at TP6 as the NLT met the RECIST 1.1 criteria for PD with ≥20% increase in iSOD and ≥ 5 mm increase from nadir.
- iBOR will be iPR. TP6 will be used as event date for iPFS/iTTP/iDOR.

16.2.5.4 Scenario 4: Confirmation of progression (iCPD) following missing assessments after iUPD

	Baseline	TP1	TP2	TP3	TP4	TP5
TL (SOD mm)	100	50	50	55	55	60
NTL	Present	UC	UC	UC	UC	NE
NLT (# of NLT/ iSOD mm)	-	-	-	-	-	-
NLNT	-	-	+	UC	NE	UC
TP response (RECIST)	-	PR	PD	PD	PD	PD
TL response (iRECIST)	-	iPR	iPR	iPR	iPR	iUPD
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NE
NLT response (iRECIST)	-	-	-	-	-	-
NLNT response (iRECIST)	-	-	iUPD	iUPD	NE	iUPD
TP response (iRECIST)	-	iPR	iUPD	iUPD	NE	iCPD

TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non- Target; TP = Time-point; NE = Not evaluated/evaluable; UC = Unchanged;
+ denotes appearance of one new lesion

- RECIST/iRECIST PR/iPR at TP1 due to due to ≥30% decrease in target lesion SOD compared to baseline.
- RECIST/iRECIST PD/iUPD at TP2 due to appearance of a NLNT.
- iRECIST iUPD at TP3 as there is no iCPD and no reset of response.
- NE at TP4 due to NLNT was not evaluated and iCPD was not observed based on target/non-target lesions.
- iCPD at TP5 as progression in target lesions based on RECIST 1.1.
- iBOR will be iSD. TP2 will be used as event date for iPFS/iTTP/iDOR.

16.2.5.5 Scenario 5: iSD after prior iUPD and subsequent recurrence of iUPD

	Baseline	TP1	TP2	TP3	TP4	TP5	TP6	TP7
TL (SOD mm)	100	80	80	75	64	68	68	80
NTL	Present	UC	UC	UC	UC	UC	UC	UC
NLT (# of NLT/ iSOD mm)	-	+/10	+/10	+/10	+/12	+/15	+/15	+/15
NLNT	-	-	-	-	-	-	-	+
TP	-	PD	PD	PD	PD	PD	PD	PD

	Baseline	TP1	TP2	TP3	TP4	TP5	TP6	TP7
response (RECIST)								
TL response (iRECIST)	-	iSD	iSD	iSD	iPR	iPR	iPR	iUPD
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
NLT response (iRECIST)	-	iUPD	iUPD	iSD	iSD	iUPD	iUPD	iUPD
NLNT response (iRECIST)	-	-	-	-	-	-	-	iUPD
TP response (iRECIST)	-	iUPD	iUPD	iSD	iPR	iUPD	iUPD	iCPD
TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non- Target; TP = Time-point; UC = Unchanged; + denotes appearance of one new lesion								

- RECIST/iRECIST PD/iUPD at TP1 due to NLT
- iUPD at TP2 as there is no change in lesions from TP1
- iSD at TP3 based on RECIST 1.1 as iUPD was not confirmed and target lesions met SD criteria per RECIST 1.1 even though NLT remained unchanged. The status is reset with this iSD. Previous iUPD will no longer be considered.
- iPR at TP4 as target lesions met PR criteria per RECIST 1.1 even though NLT changed but did not meet the criteria for iUPD (≥ 20% increase in iSOD and ≥ 5 mm increase from nadir).
- Recurrence of iUPD at TP5 as the NLT met the RECIST 1.1 criteria for PD (≥20% increase in iSOD and ≥ 5 mm increase from nadir).
- iUPD remained at TP6 as there was no change in lesions compared to TP5.
- iCPD at TP7 due to appearance of NLNT confirming TP6 iUPD.
- iBOR will be iSD as iPR was not confirmed. TP5 will be used as event date for iPFS/iTTP/iDOR.

16.2.5.6 Scenario 6: iCPD due to further worsening of target lesions

	Baseline	TP1	TP2	TP3	TP4
TL (SOD mm)	100	120	122	124	126
NTL	Present	UC	UC	UC	UC
NLT (# of NLT/ iSOD mm)	-	-	-	-	-
NLNT	-	-	-	-	-
TP response (RECIST)	-	PD	PD	PD	PD
TL response (iRECIST)	-	iUPD	iUPD	iUPD	iCPD

NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
NLT response (iRECIST)	-	-	-	-	-
NLNT response (iRECIST)	-	-	-	-	-
TP response (iRECIST)	-	iUPD	iUPD	iUPD	iCPD
TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non-Target; TP = Time-point; UC = Unchanged;					

- RECIST/iRECIST PD/iUPD at TP1 as PD was met per RECIST 1.1
- iRECIST iUPD at TP2 and TP3 as iUPD was not confirmed and PD criteria was still met per RECIST 1.1
- iCPD at TP4 due to ≥ 5 mm increase from TP1 where iUPD was first observed.
- iBOR will be iCPD. TP1 will be used as event date for iPFS/iTTP/iDOR.

16.2.5.7 Scenario 7: Resolution of some new lesions

	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
TL (SOD mm)	100	70	72	72	75	75
NTL	Present	UC	UC	UC	UC	UC
NLT (# of NLT/ iSOD mm)	-	++/ 37	+*/ 25	NE	+*/25	+*/30
NLNT	-	-	-	-	+	UC
TP response (RECIST)	-	PD	PD	PD	PD	PD
TL response (iRECIST)	-	iPR	iSD	iSD	iSD	iSD
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
NLT response (iRECIST)	-	iUPD	iSD	NE	iSD	iCPD
NLNT response (iRECIST)	-	-	-	-	iUPD	iUPD
TP response (iRECIST)	-	iUPD	iSD	NE	iUPD	iCPD
TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non-Target; TP = Time-point; NE = Not evaluated/evaluable; UC = Unchanged; + denotes appearance of one new lesion; * the new lesion resolved						

- RECIST/iRECIST PD/iUPD at TP1 due to first appearance of NLTs.
- iRECIST iSD at TP2 as TL met SD criteria per RECIST 1.1 with a decrease of > 5 mm in iSOD even though one of the NLT remained and one of them resolved. The status is reset with this iSD. Previous iUPD will no longer be considered.
- NE at TP3 as NLTs were not evaluated and iUPD not observed in evaluated categories.
- Recurrence of iUPD at TP4 due to appearance of NLNT.

- iCPD at TP5 due to NLT iSOD further increase of ≥ 5 mm from TP4, where iUPD was observed.
- iBOR will be iSD. TP4 will be used as event date for iPFS/iTTP/iDOR.

16.2.5.8 Scenario 8: iUPD continues due to no change in target lesions

	Baseline	**TP1**	**TP2**	**TP3**	**TP4**
TL (SOD mm)	100	72	72	69	66
NTL	Present	UC	UC	UC	UC
NLT (# of NLT/ iSOD mm)	-	-	-	-	-
NLNT	-	+	UC	UC	UC
TP response (RECIST)	-	PD	PD	PD	PD
TL response (iRECIST)	-	iSD	iSD	iPR	iPR
NTL response (iRECIST)	-	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD	NiCR/NiUPD
NLT response (iRECIST)	-	-	-	-	-
NLNT response (iRECIST)	-	iUPD	iUPD	iUPD	NiCR/NiUPD
TP response (iRECIST)	-	iUPD	iUPD	iUPD	iPR
TL = Target Lesions; NTL = Non-target Lesions; NLT = New Lesions Target; NLNT = New Lesions Non-Target; TP = Time-point; NE = Not evaluated/evaluable; UC = Unchanged; + denotes appearance of one new lesion					

- RECIST/iRECIST PD/iUPD at TP1 due to NLNT.
- iUPD at TP2 as there was no change in lesions from TP1.
- iUPD at TP3 as there was no change in TL (< 5 mm change in SOD from TP2) and there was no change in NTL and NLNT.
- iPR at TP4 as PR criteria per RECIST 1.1 was met with a change > 5 mm in SOD even though NLNT remained unchanged. The status is reset with this iPR. Previous iUPD will no longer be considered.
- iBOR will be iSD. TP4 will be used as censoring date for iPFS/iTTP/iDOR.

16.3 Appendix 3: Statistical Details for Safety Run-in 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 and respective dosing decisions for some hypothetical data scenarios.

16.3.1 Statistical Models

For each of the cohort (cohort A: pemetrexed+carboplatin, cohort B: pemetrexed+cisplatin, cohort C: carboplatin+paclitaxel), a separate statistical model will comprise of single-agent toxicity parts and interaction parts to describe two-way drug safety interactions. Of note pembrolizumab in combination with the platinum-based doublet chemotherapy will be considered as a single agent in each of the model. The dose de-escalation part of this study will be guided by a Bayesian analysis of dose limiting toxicity (DLT) data. The Bayesian analysis will be based on a model with 3 parts, representing:

- Single agent canakinumab toxicity
- Pembrolizumab in combination with platinum-based doublet chemotherapy toxicity
- Interaction between canakinumab and pembrolizumab combined with platinum-based doublet chemotherapy

16.3.1.1 Single agent part

Let $\pi_1(d_1)$ be the risk of DLT for Canakinumab given as a single agent Q3W at dose d_1; $\pi_{2k}(d_{2k})$ be the risk of DLT for platinum-based doublet chemotherapy given as a combined therapy with pembrolizumab at dose d_{2k}.

These single agent dose-DLT models are logistic:

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

Pembrolizumab+platinum-based doublet chemotherapy:
$\text{logit}(\pi_{2k}(d_{2k}))=\log(\alpha_{2k})+\beta_{2k}\log(d_{2k}/d_{2k}^*)$

where k corresponds to the k^{th} model (k=1, 2, 3), d_1^*= 200 mg Q3W and

- for cohort A (1st model), d_{21}* (reference dose of each drug) = 200 mg for pembrolizumab, 500 mg/m^2 for pemetrexed and carboplatin AUC 5 mg/mL*min

- for cohort B (2nd model), d_{22}* (reference dose of each drug) = 200 mg for pembrolizumab, 500 mg/m^2 for pemetrexed and cisplatin 75 mg/m^2

- for cohort C (3rd model), d_{23}* (reference dose of each drug) = 200 mg for pembrolizumab, AUC 6 mg/mL*min for carboplatin and 200 mg/m^2 for paclitaxel

are used to scale the doses of canakinumab, pembrolizumab in combination with platinum-based doublet chemotherapy, respectively. Hence, α_1 and α_{2k} (>0) are the single-agent odds of a DLT at 200mg Q3W and at the corresponding fixed doses of pembrolizumab with each platinum-based doublet chemotherapy as described above, respectively; β_1 and β_{2k} (>0) are the increase in the log-odds of a DLT by a unit increase in log-dose.

16.3.1.2 Interaction

Under no interaction, the risk of a DLT at dose d_1 of canakinumab and dose d_{2k} of platinum-based doublet chemotherapy in combination with pembrolizumab is:

$\pi^0_{12k}(d_1, d_{2k}) = 1- (1 - \pi_1 (d_1))(1-\pi_{2k} (d_{2k}))$

To allow for interaction between canakinumab and pembrolizumab in combination with platinum-based doublet chemotherapy, an odds multiplier is introduced. The risk of DLT for combination dose (d_1, d_{2k}) is then given by:

$odds(\pi_{12k} (d_1, d_{2k}))=exp(\eta_{12k}\times d_1/(d_1^*)\times d_{2k}/(d_{2k}^*))\times odds(\pi_{12k}^0 (d_1, d_{2k}))$

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

16.3.1.3 Prior specifications

The Bayesian approach requires the specification of prior distributions for all models parameters, which include the single agent parameters $\log(\alpha_1)$, $\log(\beta_1)$ for canakinumab, and $\log(\alpha_{2k})$, $\log(\beta_{2k})$ for pembrolizumab plus the platinum-based doublet chemotherapy, and the interaction parameter η_{12k}, A meta-analytic-predictive (MAP) approach was used to derive the prior distribution for the single-agent model parameters for canakinumab. A weakly informative prior is derived for the single-agent model parameters for pembrolizumab plus the platinum-based doublet chemotherapy.

Prior distribution for the logistic parameters

A MAP approach was used to incorporate the dose-DLT data from canakinumab. To make the prior more robust, an additional mixture component corresponding to high toxicity was introduced.

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

The aim of the MAP approach is to derive a prior distribution for the logistic parameters $(\log(\alpha^*),\log(\beta^*))$ 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,…,S). The corresponding probability of a DLT is π_{ds}. The model specifications for the derivation of the MAP prior are as follows:

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

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

$(\log(\alpha_s),\log(\beta_s))| \mu,\psi \sim BVN(\mu,\psi), s=1,\ldots,S$

$(\log(\alpha^*),\log(\beta^*)) | \mu,\psi \sim BVN(\mu,\psi)$

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, $(\log(\alpha^*),\log(\beta^*))$, is the predictive distribution

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

Since the predictive distribution is not available analytically, Markov chain Monte Carlo (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).

Single agent canakinumab

For canakinumab, this study uses a mixture prior consisting of four components. Component 1, 2 and 3 are derived based on dose-DLT data from canakinumab oncology study [CACZ885I2202] by MAP approach. The assigned total weight for Component 1, 2 and 3 is 90%. Component 4 allows for a higher toxicity case. The assigned weight for Component 4 is 10%.

- **Component 1, 2 and 3**

For the MAP model for canakinumab, reference dose d_2^*=200 mg Q3W is used, and data from S=1 historical study is available.

Canakinumab dose levels in Q3W and Q6W dosing schedule are converted to Q4W by finding out the dose level in Q4W which provides equivalent area under the curve (AUC 0-6weeks) for dose levels in Q3W and Q6W. The simulated PK profiles of canakinumab at 200 mg Q3W and 300 mg Q4W are comparable PK for Canakinumab. Hence, 200 mg on Q3W regimen is equivalent to 300 mg on Q4W regimen and 200 mg on Q6W is equivalent to 150 mg on Q4W regimen.

After the dose conversion is performed as described above, canakinumab 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 moderate between trial heterogeneity, and (2) their uncertainty (95% prior interval) cover plausible between-trial standard deviations (Neuenschwander 2014). Canakinumab 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 16-11.

Table 16-11 Prior distributions for the parameters of the MAP model used to derive the prior for the single-agent canakinumab 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 = 0.250, sd = log(2)/1.96)
τ_2	log-normal(mean = 0.125, sd = log(2)/1.96)
ρ	uniform(-1,1)

Historical data is presented in Table 16-12.

Table 16-12 Historical data from [CACZ885I2202] for canakinumab single agent

Canakinumab Q4W dose level (mg)	Converted to dose level in Q8W (mg)	Number of patients completed 4 months	Number of patients with AEs leading to permanent treatment discontinuation in first 4 months	Number of patients in total
5	10	87	0	87
15	30	93	1	94
50	100	84	0	84
150	300	90	1	91

- **Component 4:**

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

- For the intercept parameter $\log(\alpha_1)$, 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_1^*= 200 mg Q3W. By setting the standard deviation =2, the respective 95% a-priori interval for probability of DLT at dose 200 mg Q3W is wide (0.7%, 94.4%), which represents weak prior information.

- For the log-slope parameter $\log(\beta_1)$, 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 $3^{\beta 1}$.

- The Component 4 is set to be (-1.099, 0, 2, 1, 0)

Single agent: Pembrolizumab in combination with platinum-based doublet chemotherapy

Doses for each of the drugs are fixed at:

-200 mg Q3W for pembrolizumab, 500mg/m2 for pemetrexed and AUC 5 for carboplatin for first model (k=1)

-200 mg Q3W for pembrolizumab, 500 mg/m2 for pemetrexed and 75 mg/m2 for cisplatin for second model (k=2)

-200 mg Q3W for pembrolizumab, AUC 6 carboplatin and 200 mg/m2 for paclitaxel for third model (k=3)

A weakly prior will be assumed according to a DLT rate of 15% for k=1st model, 10% for k=2nd model and 20% for k=3rd model. The median for the prior distribution of $\log(\beta_{2k})$ is set to 0, to correspond to a doubling of dose leading to a doubling of the odds of DLT. The standard

deviation for $\log(\alpha_{2k})$ is derived assuming that there is 90% probability, 95% probability, 80% probability that the DLT rate is lower than 25% for the 1st model, 2nd and 3rd model, respectively. The standard deviation for $\log(\beta_{2k})$ is 1. The correlation between the two standard deviations is $\rho=0$.

Interaction parameter: weakly prior distribution

Based on the available information, the interaction is centered at a 0% increase in odds of DLT platinum-based doublet chemotherapy in all 3 models (k=1, 2, 3) and under each canakinumab dosing regimen. However, in all cases, considerable uncertainty remains as to the true interaction, and normal priors are used that allow for both synergistic and antagonistic toxicity. The following assumptions will be used for interaction parameters for the 3 models:

- η_{12k} is normally distributed and centered at 0, i.e. 0% increase in odds of DLT over independence at the combination starting dose
- 97.5th percentile is log(2.5), i.e. 2.5-fold increase in odds of DLT over independence at the combination starting dose

16.3.2 Summary of prior distributions

The prior distributions of the model parameters are summarized in Table 16-13.

The prior summaries for DLT rates are summarized in Table 16-14.

Table 16-13 Prior distribution for the 3 models parameters

Parameter	Mean	Standard deviations	correlation	weight
Single agent Canakinumab prior applied for the 3 models				
BVN Mixture ($\log(\alpha_1, \beta_1)$)				
Component 1 (MAP prior)	(-3.847 , -0.475)	(0.651, 0.493)	0.176	0.427
Component 2 (MAP prior)	(-3.128 , 0.018)	(0.732, 0.425)	0.463	0.246
Component 3 (MAP prior)	(-4.736 , -1.105)	(0.737, 0.696)	0.004	0.227
Component 4 (high toxicity)	(-1.099 , 0)	(2, 1)	0	0.100
1st model				
Single agent Pembrolizumab in combination with pemetrexed plus carboplatin chemotherapy				
BVN Mixture ($\log(\alpha_{21}, \beta_{21})$)				
Weakly informative prior	(-1.735 , 0)	(0.496, 1.000)	0	1.000
Interaction parameter				
Normal	0	0.468	N/A	N/A
η_{121}				
2nd model				

Single agent Pembrolizumab in combination with pemetrexed plus cisplatin chemotherapy				
BVN Mixture ($\log(\alpha_{22}, \beta_{22})$)				
Weakly informative prior	(-2.197 , 0)	(0.668, 1.000)	0	1.000
Interaction parameter				
Normal				
η_{122}	0	0.468	N/A	N/A
3rd model				
Single agent Pembrolizumab in combination with carboplatin plus paclitaxel chemotherapy				
BVN Mixture ($\log(\alpha_{23}, \beta_{23})$)				
Weakly informative prior	(-1.386 , 0)	(0.342, 1.000)	0	1.000
Interaction parameter				
Normal				
η_{123}	0	0.468	N/A	N/A

Table 16-14 Summary of prior distribution of DLT rates

Pembrolizumab (Q3W) in combination with :	**Prior probabilities that P(DLT) is in the interval :**			**Mean**	**SD**	**Quantiles**		
	[0, 0.16)	**[0.16, 0.33)**	**[0.33,1]**			**2.5%**	**50%**	**97.5%**
	In combination with Canakinumab 200 mg Q6W							
1st model : Pemetrexed+carboplatin	0.449	0.477	**0.074**	0.192	0.111	0.068	0.169	0.471
2nd model : Pemetrexed + cisplatin	0.685	0.262	**0.053**	0.149	0.115	0.038	0.120	0.453
3rd model : Carboplatin + paclitaxel	0.180	0.714	**0.106**	0.236	0.104	0.111	0.218	0.487
	In combination with Canakinumab 200 mg Q3W							
1st model : Pemetrexed + carboplatin	0.405	0.449	**0.145**	0.218	0.144	0.057	0.184	0.634
2nd model : Pemetrexed +cisplatin	0.598	0.302	**0.100**	0.175	0.145	0.034	0.135	0.616
3rd model : carboplatin + paclitaxel	0.220	0.563	**0.217**	0.260	0.141	0.087	0.232	0.654
Note : the P(DLT) on the excessive toxicity interval is highlighted in bold.								

16.3.3 Hypothetical on-study scenarios

To illustrate the performance of the Bayesian models used to guide dose de-escalation, hypothetical DLT observed scenarios following the provisional dose levels as defined previously are shown for each chemotherapy regiment (pemetrexed plus carboplatin, pemetrexed plus cisplatin and carboplatin plus paclitaxel regimen) in Table 16-15, Table 16-16 and Table 16-17. In each table, the dose that can be used in the next cohort of patients is shown. This dose is determined using the model based assessment of the risk of DLT in future patients and the dose de-escalation rules

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

Table 16-15 Dose decisions recommended by BLRM for pemetrexed plus carboplatin chemotherapy regimen under EWOC

Scenario	Canakinumab regimen with Pembrolizumab in combination with pemetrexed+carboplatin chemotherapy	Number of		Next dose level			
		patients	DLTs	Canakinumab regimen with Pembrolizumab in combination with pemetrexed+carboplatin chemotherapy	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
1	200 mg Q3W	6	0	200 mg Q3W	0.324	0.018	0.131
2	200 mg Q3W	6	1	200 mg Q3W	0.5	0.065	0.173
3	200 mg Q3W	6	2	200 mg Q3W	0.594	0.178	0.225
4	200 mg Q3W	6	3	200 mg Q3W	0.530	0.378	0.290
5	200 mg Q3W	6	3				
	200 mg Q6W	6	0	200 mg Q6W	0.665	0.042	0.193
6	200 mg Q3W	6	3				
	200 mg Q6W	6	1	200 mg Q6W	0.737	0.100	0.223
7	200 mg Q3W	6	3				
	200 mg Q6W	6	2	200 mg Q6W	0.724	0.195	0.254
8	200 mg Q3W	6	3				
	200 mg Q6W	6	3	200 mg Q6W	0.610	0.358	0.294
Note that the overdose criterion is defined as P(excessive toxicity) < 0.25.							

Table 16-16 Dose decisions recommended by BLRM for pemetrexed plus cisplatin chemotherapy regimen under EWOC

Scenario	Canakinumab regimen with Pembrolizumab in combination with pemetrexed+cisplatin chemotherapy	Number of		Next dose level			
		patients	DLTs	Canakinumab regimen with Pembrolizumab in combination with pemetrexed+cisplatin chemotherapy	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
1	200 mg Q3W	6	0	200 mg Q3W	0.168	0.008	0.095
2	200 mg Q3W	6	1	200 mg Q3W	0.352	0.040	0.137

Scenario	Canakinumab regimen with Pembrolizumab in combination with pemetrexed+cisplatin chemotherapy	Number of		Next dose level			
		patients	DLTs	Canakinumab regimen with Pembrolizumab in combination with pemetrexed+cisplatin chemotherapy	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
3	200 mg Q3W	6	2	200 mg Q3W	0.504	0.143	0.195
4	200 mg Q3W	6	3	200 mg Q3W	0.498	0.355	0.275
5	200 mg Q3W	6	3				
	200 mg Q6W	6	0	200 mg Q6W	0.471	0.030	0.16
6	200 mg Q3W	6	3				
	200 mg Q6W	6	1	200 mg Q6W	0.612	0.087	0.198
7	200 mg Q3W	6	3				
	200 mg Q6W	6	2	200 mg Q6W	0.645	0.206	0.244
8	200 mg Q3W	6	3				
	200 mg Q6W	6	3	200 mg Q6W	0.545	0.396	0.299
Note that the overdose criterion is defined as P(excessive toxicity) < 0.25.							

Table 16-17 Dose decisions recommended by BLRM for carboplatin plus paclitaxel chemotherapy regimen under EWOC

Scenario	Canakinumab regimen with Pembrolizumab in combination with carboplatin+paclitaxel chemotherapy	Number of		Next dose level			
		patients	DLTs	Canakinumab regimen with Pembrolizumab in combination with carboplatin+paclitaxel chemotherapy	P(Target toxicity)	P(excessive toxicity)	Median P(DLT)
1	200 mg Q3W	6	0	200 mg Q3W	0.512	0.042	0.170
2	200 mg Q3W	6	1	200 mg Q3W	0.635	0.110	0.210
3	200 mg Q3W	6	2	200 mg Q3W	0.639	0.239	0.255
4	200 mg Q3W	6	3	200 mg Q3W	0.523	0.430	0.310
5	200 mg Q3W	6	3				
	200 mg Q6W	6	0	200 mg Q6W	0.837	0.068	0.229
6	200 mg Q3W 200 mg Q6W	6 6	3 1	200 mg Q6W	0.825	0.126	0.25
	200 mg Q6W	6	1	200 mg Q6W	0.825	0.126	0.25
7	200 mg Q3W	6	3				
		6	2	200 mg Q6W	0.761	0.218	0.273
8	200 mg Q3W	6	3				
		6	3	200 mg Q6W	0.649	0.342	0.298
Note that the overdose criterion is defined as P(excessive toxicity) < 0.25.							

For all 3 chemotherapy regimens :

-If <=2 DLTs are observed in the first 6 evaluable patients, the probability of excessive toxicity (i.e. DLT rate of ≥ 33%) with dosing regimen of canakinumab 200 mg Q3W is < 25%, satisfying

the EWOC criteria. In this case, it would be recommended to continue with Q3W dosing of Canakinumab

-If 3 or more DLTs are observed in the first 6 evaluable patients, the probability of excessive toxicity with dosing regimen of canakinumab 200 mg Q3W does not satisfy the EWOC criteria. In this case, it would be recommended to test the lowest dose regimen (i.e. canakinumab 200 mg Q6W)

If 3 or more DLTs are observed in the first 6 evaluable patients at the lowest dose regimen of canakinumab (i.e. canakinumab 200 mg Q6W), the probability of excessive toxicity does not satisfy the EWOC criteria. In this case, it would be recommended not to proceed with the regimen.

16.3.4 References (available upon request)

Akaike H (1974) A new look at the statistical model identification. IEEE Transactions on Automatic Control; 19::716-23.

Dempster AP, Laird NM, Rubin DB (1977) Maximum Likelihood from Incomplete Data via the EM Algorithm. J R Stat Soc Series B Stat Methodol; 39:1-38.

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

16.4 Appendix 4: Medications to be used with caution with paclitaxel/nab-paclitaxel while on study

Table 16-18 Drugs to be used with caution with paclitaxel/nab-paclitaxel while on study

Strong CYP3A4/5 inhibitors			
Macrolide antibiotics:	**Antivirals:**	**Antifungals:**	**Others:**
clarithromycin	indinavir	itraconazole	conivaptan
telithromycin	lopinavir/ritonavir	ketoconazole	elvitegravir
troleandomycin	nelfinavir	posaconazole	mibefradil
	ritonavir	voriconazole	nefazodone
	indinavir/ritonavir		cobicistat
	saquinavir		grapefruit juice
	saquinavir/ritonavir		
	telaprevir		
	tipranavir/ritonavir		
	danoprevir/ritonavir		
	elvitegravir/ritonavir		
	boceprevir		
Strong CYP2C8 inhibitors			
gemfibrozil			
Strong CYP3A/5 inducers			
avasimibe	carbamazepine	phenobarbital	phenytoin
rifabutin	rifampin	St. John's wort	mitotane

enzalutamide			
Source: This list is adapted from Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: April 2015) which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling (February 2012), and the University of Washington's Drug Interaction Database. The lists provided may not be exhaustive.			

16.5 Appendix 5: Medications to be used with caution with canakinumab while on study

Table 16-19 CYP3A substrates with narrow therapeutic index, or sensitive CYP2C9 substrates with narrow therapeutic index**

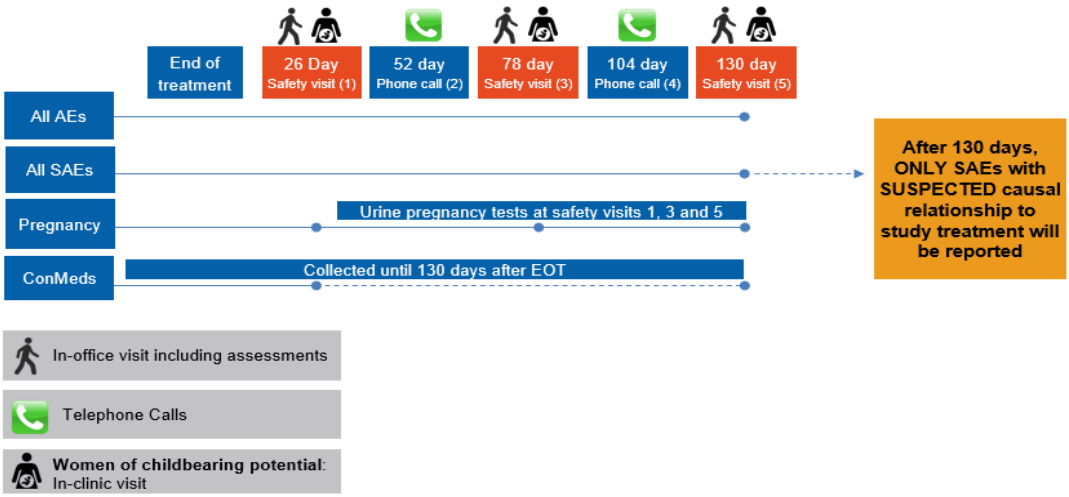
CYP2C9 substrates with narrow therapeutic index			
warfarin	phenytoin		
CYP3A4/5 substrates with narrow therapeutic index			
astemizole*	diergotamine	pimozide	alfentanil
cisapride*	ergotamine	quinidine*	terfenadine*
cyclosporine	fentanyl	tacrolimus	sirolimus

*Compounds known to increase QTc interval that are also primarily metabolized by CYP3A4/5.

For an updated list of CYP2C9 substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.

**Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

16.6 Appendix 6: Safety follow-up flow chart (post implementation of protocol amendment 05)



16.7 Appendix 7: Pembrolizumab Dose Modification Guidelines

Table 16-20 Dose Modification and Toxicity management Guidelines for Immune-related Adverse Events associated with Pembrolizumab

General instructions:

1. Corticosteroids taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should beinitiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurr·ent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently dis continue		
AST /ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value retumed to baseline or is stable).

General instructions:

1. Corticosteroids taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should beinitiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 3 or 4	Permanently dis continue	• Administer corticosteroids (initi al dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (TIDM) or Hyperglyce mia	Newly onsetT1DM or Grade 3 or 4 hyperglycemia associated withevidence of beta-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysit is	Grade 2	Withhold	• Administer corticosteroids and initiate harmonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyro idism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroi dism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (initi al dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

General instructions:

1. Corticosteroids taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should beinitiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	• Based on type and severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold ordiscontinue basedon the type of event. Events that require discontinuation include and not limited to: Gullain- Barre Syndrome, encephalitis		
	Grade 4 orrecurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
Note: For participants with Grade 3 or 4 immune-related endocrinopathy where withholdof pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)