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ACZ885

Clinical Trial Protocol CACZ885V2201C / NCT03968419

A randomized, open-label, phase II study of canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in subjects with resectable non-small cell lung cancer (CANOPY-N)

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Table of contents

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[redacted]

[redacted]

List of tables

List of figures

[redacted]

[redacted]

List of abbreviations

ADA	Anti-Drug Antibodies
ADR	Adverse Drug Reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	alkaline
ALP	alkaline phosphatase
alpha-FP	alpha fetoprotein
ALT	Alanine transaminase
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BOR	Best Overall Response
CAPS	Cryopyrin Associated Periodic Syndromes
CD-transferrin	Carbohydrate Deficient-transferrin
CDS	Core Data Sheet (for marketed drugs)
CFR	Code of Federal Regulation
CHF	Congestive Heart Failure
Cmax	Maximum concentration
CMO&PS	Chief medical office and patient safety
CMV	Cytomegalovirus
CR	complete response
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CRS	Case Retrieval Strategy
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CV	coefficient of variation
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interactions
DFS	Disease Free Survival
DILI	Drug Induced Liver Injury
DNA	Deoxyribonucleic acid
e.g.	exempli gratia
EBV	Epstein-Barr Virus

[redacted]

EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EMA	European medicines agency
EOT	End of Treatment
ERCP	Endoscopic Retrograde Cholangiopancreatography
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FFPE	Formalin-fixed paraffin embedded
FMF	Familial Mediterranean Fever
FPFV	First patient first visit
G-CSF	Granulocyte Colony-Stimulating Factor
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl-transferase
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
IAC	Infection adjudication committee
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use’
IEC	Independent Ethics Committee
IG	Immunogenicity
IgA	Immunoglobulin A

[redacted]

IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IHC	Immunohistochemistry
IL-1β	Interleukin-1β
IN	Investigator Notification
INR	International Normalized Ratio
IO	Immuo-Oncology
IQR	Interquartile Range
irAE	Immune-related adverse events
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention to treat
IUD	Intrauterine Device
IUS	Intrauterine System
LDH	lactate dehydrogenase
LFT	Liver function test
LPLV	Last patient last visit
MACE	Major Adverse Cardiovascular Events
MCA	methylcholanthrene
MCV	Mean Corpuscular Volume
MDSCs	Myeloid Derived Suppressor Cells
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram(s)
MKD	Mevalonate Kinase Deficiency
mL	milliliter(s)
MPR	Major Pathological Response
MRI	Magnetic Resonance Imaging
NASH	Nonalcoholic steatohepatitis
NF-κB	Nuclear Factor Kappa Beta
NIMP	Non-investigational medicinal Product
NSCLC	Non-small cell lung cancer
o.d.	once a day
ORR	Overall Response Rate
OS	Overall Survival
PAS	Pharmacokinetic Analysis Set
PD	pharmacodynamic(s)
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	pharmacokinetic(s)

[redacted]

PR	partial response
PS	Performance Status
PT	Prothrombin Time
Q3W	Every 3 weeks
QMS	Quality Management System
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RoW	Rest of World
RP2D	Recommended Phase 2 Dose
s.c.	subcutaneous
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	serum creatinine
SD	standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1D	Type 1 Diabetes
T3	triiodothyronine
T4	Thyroxine
TAM	Tumor Associated Macrophages
TB	Tuberculosis
TBIL	Total Bilirubin
TCR	T Cell Receptor
TFQ	Trial Feedback Questionnaire
TNF	Tumor Necrosis Factor
TNFα	Tumor Necrosis Factor alpha
TPS	Tumor Proportion Score
TRAPS	Tumor Necrosis Factor Receptor Associated Periodic Syndrom
TSH	Thyroid-Stimulating Hormone
TTP	Time to progression
ULN	upper limit of normal
UNK	Unknown
US	United States
USPI	US-Package Insert
VATS	Video-Assisted Thoracic Surgery
VEGF	Vascular Endothelial Growth Factor
Vs	versus
[redacted]	[redacted]
WHO	World Health Organization

[redacted]

WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug (active or placebo) 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
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 drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
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	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned

[redacted]

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
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 treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not want/allow any further visits or assessments, and does not want any further study related contact/collection of personal data

[redacted]

Protocol summary

Protocol number	CACZ885V2201C
Full Title	A randomized, open-label, phase II study of canakinumab or pembrolizumab as monotherapy or in combination as neoadjuvant therapy in subjects with resectable non-small cell lung cancer (CANOPY-N)
Brief title	This study will evaluate the effect of canakinumab or pembrolizumab given as monotherapy or in combination as neo-adjuvant treatment for subjects with early stages NSCLC.
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this randomized, open-label, phase II study is to evaluate the major pathological response (MPR) rate of canakinumab given as a neoadjuvant treatment, either as single agent or in combination with pembrolizumab, in addition to evaluate the MPR of pembrolizumab as a single agent. Additionally the dynamics of the tumor microenvironment changes on treatment by comparing pre-, on- and post-treatment samples will be evaluated.
Primary Objective(s)	To assess the MPR rate (≤ 10% of residual viable tumor cells) on the resected specimen at the time of surgery in all subjects randomized to canakinumab alone or in combination with pembrolizumab
Secondary Objectives	• To assess overall response rate (ORR) in randomized subjects treated with canakinumab or pembrolizumab as monotherapy or in combination • To assess surgical feasibility rate in each treatment arm based on randomized subjects • To assess the MPR rate at the time of surgery in (a) all subjects randomized to pembrolizumab monotherapy arm, (b) all randomized subjects based on local review in each treatment arm and (c) to estimate the difference in MPR and posterior probability of the difference in MPR ≥ 10% between subjects randomized to canakinumab + pembrolizumab combination and pembrolizumab alone • To assess the prevalence and incidence of immunogenicity (IG) anti-drug antibodies (ADA) of canakinumab and pembrolizumab • To assess the pharmacokinetics (PK) of canakinumab and pembrolizumab as monotherapy and in combination • To evaluate safety and tolerability of canakinumab and pembrolizumab as monotherapy and in combination • To assess the relationship between key blood or tissue based biomarkers and MPR
Study design	This is a phase II, randomized, open-label study evaluating efficacy and safety of canakinumab or pembrolizumab monotherapy or in combination as neoadjuvant treatment. Approximately 110 subjects will be randomized in a 2:2:1 ratio to one of the treatment arms (canakinumab alone or canakinumab in combination with pembrolizumab or pembrolizumab alone). Randomization will be stratified by histology (squamous vs non-squamous)

[redacted]

Population	110 adult subjects, male and female with resectable non-small cell lung cancer (NSCLC)
Key Inclusion criteria	Histologically confirmed NSCLC stage IB-IIIA (per American Joint Committee on Cancer (AJCC) 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors. Subject must be eligible for surgery and with a planned surgical resection in approximately 4 to 6 weeks (from the first dose of study treatment). A mandatory newly obtained tissue biopsy from primary site is required for study enrollment. An archival biopsy is also acceptable if obtained up to 5 months before first day of study treatment and if the subject did not go through antineoplastic systemic therapies between biopsy collection date and beginning of study treatment. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
Key Exclusion criteria	Subjects with unresectable or metastatic disease. All subjects should have brain imaging (either Magnetic Resonance Imaging (MRI) brain or Computed Tomography (CT) brain with contrast) prior to enrollment to exclude brain metastasis. History of severe hypersensitivity reactions to monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction. Presence or history of a malignant disease that has been diagnosed and/or required therapy within the past 3 years. 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. Subjects who received prior systemic therapy (including chemotherapy, other anti-cancer therapies and any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) in the past 3 years before screening.
Study treatment	In this study, the “study treatment” refers to both canakinumab and pembrolizumab study drugs administered either as monotherapy or in combination of study drugs: canakinumab plus pembrolizumab Subjects will receive 2 doses of canakinumab (200 mg s.c. Q3W) alone or in combination with pembrolizumab or two doses of pembrolizumab as single agent (200 mg i.v. Q3W).
Efficacy assessments	**MPR:** Response will be assessed centrally at the time of surgery (by number of subject with ≤ 10% residual viable cancer cells) **Radiology tumor assessments:** by investigator (RECIST 1.1) at screening and one before surgery.
Key safety assessments	• Physical examination • ECOG PS • Body weight and vital signs • Laboratory assessments, including hematology, chemistry, coagulation, thyroid function, hepatitis testing and urinalysis • Pregnancy tests for women of child-bearing potential (serum pregnancy test at screening for all female subjects) • Adverse events (AEs) the severity, the relationship with to study treatment and the seriousness
Data analysis	**Primary endpoint:**

[redacted]

	The primary endpoint is MPR rate, defined as the percentage of subjects with ≤ 10% residual viable cancer cells. The analysis of primary endpoint is described by the following five attributes: 1. The **target population** is defined as all randomized patients who are histologically confirmed NSCLC stage IB-IIIA (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors 2. The **primary variable** is the percentage of subjects with a major pathological response (defined as ≤ 10% residual viable cancer cells per central review). Any patient who has >10% residual viable cancer cells, or starts new antineoplastic therapy medication prior to surgery, or does not have the surgery performed, is considered as a non-responder 3. The **study treatment** is canakinumab as monotherapy or in combination with pembrolizumab 4. The **intercurrent events** of interest in this study are: start of new antineoplastic therapy prior to surgery and discontinuation of study treatment prior to surgery. These intercurrent events will be addressed by assessing: a. **Start of new antineoplastic therapy prior to surgery**: subject will be considered as non-responder (composite strategy) b. **Discontinuation of study treatment prior to surgery:** subject will be included in the analysis regardless of this intercurrent event (treatment-policy strategy) 5. The **summary measure** is MPR rate with its corresponding two-sided exact binomial 95% confidence interval in canakinumab alone arm and canakinumab in combination with pembrolizumab arm The proof of efficacy in canakinumab alone arm will be declared if both of the following conditions are met: • the mean of the posterior distribution of MPR is at least 30% and • the posterior probability that the MPR is ≥ 20% is at least 90% The proof of efficacy in the combination treatment arm will be declared if both of the following conditions are met: • the mean of the posterior distribution of MPR is at least 45% and • the posterior probability that the MPR is ≥ 30% is at least 90% The posterior distribution of MPR will be derived from the prior distribution and all available data from the subjects included in the Full Analysis Set (FAS). A minimally informative unimodal Beta prior will be used for MPR in each arm. Subjects who have an unknown MPR status due to surgery not being performed (including lost to follow-up or withdrawal of study consent before surgery) will be considered as non-responders when estimating MPR rate. **Secondary endpoints:** MPR rate will be assessed using the same patient population used in the primary analysis, including the strategy for handling intercurrent events (1) based on local review in all three treatment arms and (2) based on central review in pembrolizumab monotherapy arm. MPR rate for all the above specified analyses will be summarized by treatment arm along with the two-sided exact binomial 95% confidence interval.

	The difference in MPR rate between canakinumab in combination with pembrolizumab and pembrolizumab single agent arm along with the two-sided exact 95% confidence interval based on Chan and Zhang (1999) will be summarized based on central review using the same patient population used in the primary analysis, including the strategy for handling intercurrent events. The posterior probability of the difference 10% or greater in MPR rate will also calculated. Surgical feasibility rate is defined as the percentage of subjects in FAS who undergo surgery following study treatment. Surgical feasibility rate and two-sided exact binomial 95% confidence interval will be presented by treatment group. Overall response rate (ORR) is defined as the percentage of subjects in FAS with a best overall response of complete response (CR) or partial response (PR), as per local review. The best overall response will be the observed response at the assessment performed prior to surgery. ORR will be evaluated according to RECIST 1.1. ORR and two-sided exact binomial 95% confidence interval will be presented by treatment group. Subjects with a best overall response (BOR) of 'Unknown' per RECIST 1.1 will be considered as non-responders when estimating ORR.

[redacted]

Key words	ACZ885, canakinumab, pembrolizumab, NSCLC, squamous, non-squamous, MPR, hs-CRP, PD-L1, CD8, hs-IL-6, CANOPY.

[redacted]

Amendment 1 (07-Apr-2020)

Amendment rationale

As of 07-Apr-2020, 27 sites have been initiated, 25 subjects have been screened and 17 have been randomized and treated.

The main rationale for amendment 01 is:

- To implement the request from the Health Authority to modify the target population for both the primary and secondary endpoint Major Pathological Response (MPR) from "evaluable subjects" to "randomized subjects".

In addition, the following modifications have been implemented:

- The following inclusion/exclusion criteria have been added or modified in order to allow more clarity and more flexibility for the enrollment/randomization:
  - Inclusion criterion 3 is updated to reference to Appendix 16.4 which is added to clarify which stages of NSCLC are allowed according to AJCC 8th edition
  - Inclusion criterion 5 is updated to clarify that the biopsy should be taken from primary site and that the archival biopsy should not be older than 5 months. This change (i.e. 5 months) is necessary to take into account the shipment, processing of biopsies and that biopsies are only evaluable if not older than 6 months. In addition, it is clarified that aspirates will not be accepted.
  - Exclusion criterion 5 is updated to allow subjects with history of auto-immune disease or known auto-immune disease who have not required systemic therapy in the past 2 years before study entry to be enrolled in the study.
  - Exclusion criterion 7 is updated to reflect the pembrolizumab label concerning pneumonitis
  - Exclusion criterion 8 is updated to allow more flexibility concerning the adjustment of blood pressure medication
  - Exclusion criterion 15 is added to ensure subjects with severe or uncontrolled medical conditions are not enrolled in the study
- Updated Section 6.3.2 to clarify that subjects with a tumor of adenosquamous histology can be stratified as either squamous or non-squamous histology
- The EOT visit window has been changed to within 21 days after the permanent discontinuation of study treatment but before the surgery to provide more flexibility to the site and patient
- [redacted]
- Surgery details guidance is included

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 1.1.2: The reference of the KEYNOTE-042 study has been updated to "Mok et al. 2019".

[redacted]

- Section 1.2.1: The references "Chaudhuri et al 2017" and "Jayaraman et al 2019" have been added to this section, as well as further clarification.
- Section 2: Table 2-1: Primary and secondary objectives have been updated to reflect the randomized patient population for primary endpoint. [redacted]
- Section 3: The paragraph to determine whether a patient is evaluable for the study has been removed because all randomized subjects will be considered for analysis. In addition the safety follow-up timeframe has been clarified (text and Figure 3-1).
- Section 4: Table 4-1: The reference "Paesmans 2012" has been added to the randomization stratification factors rationale.
- Section 5.1: For Inclusion criterion 3 reference to Appendix 4 (Section 16.4) has been added to clarify which stages of NSCLC are eligible.
- Section 5.1: Inclusion criterion 5 has been revised to indicate that: archival biopsy is acceptable, if obtained up to 5 months instead of 6 months before first day of study treatment due to stability reason and the site of the biopsy and the type has been clarified. In addition, it is clarified that aspirates will not be accepted.
- Section 5.2: Exclusion criterion 5 has been updated to clarify the case of an active autoimmune disease.
- Section 5.2: Exclusion criterion 7 has been revised to reflect the pembrolizumab label.
- Section 5.2: Exclusion criterion 8 has been revised to provide more flexibility to adjustment of hypertensive medication.
- Section 5.2: Exclusion criterion 15 has been added to ensure subjects with severe or uncontrolled medical conditions are not enrolled in the study.
- Section 6.2.2.1: Updated to clarify that use of steroids to treat immune-related adverse events is allowed.
- Section 6.2.2.1: The information on premedication related to chemotherapy was deleted since chemotherapy is not part of the study treatment.
- Section 6.2.2.1: It has been clarified for live vaccination during study conduct, that the subject has to stop study treatment and not the trial.
- Section 6.3.2: Updated to clarify stratification for subjects with adenosquamous histology.
- Section 6.5.1.1: Language for dose modifications related to adverse reactions clarified.
- Section 6.5.1.1: Table 6-2: Added footnote clarifying exceptions to general guidance for mandatory dose modification and to provide clarity when the interruption starts and the definition of grading has been added where needed.
- Section 6.7: Sentence to refer to instruction for use of canakinumab has been added.

[redacted]

- Section 6.7.2: Table 6-4 has been updated to provide more information about the pembrolizumab dose.
- Section 7: As required by the protocol template, it has been sprecified which ICFs are used in this trial.
- Section 8: Table 8-1: End of treatment window has been changed to within 21 days after the permanent discontinuation of study treatment but before the surgery. In addition, the window for End of treatment biomarker sampling has been added.
- Section 8: Table 8-2: CT brain with contrast has been added as an alternative to Brain MRI. Blood (whole) TCR sequencing was deleted. Footnote referring to TCR sequencing was deleted and footnotes to clarify the latest time point for EOT and when biomarker blood samples should be collected were added.
- Section 8.2: Updated to clarify that serum pregnancy testing is for all female subjects at screening. In addition, a statement concerning the reason for collecting race and ethnicity has been added.
- Section 8.4: Table 8-3 has been updated to reflect that height will be collected in inches as well and weight in kilogram or pounds.
- Section 8.4.1: Table 8-4: Updated to include "pancreatic amylase (as needed)".
- [redacted]
- Section 8.5.2: Age of archival biopsy has been updated (i.e. slide cut date must be within 5 months instead of 6 months), guidance on blood sampling for end of treatment (EOT) has been clarified, TCR sequencing was deleted and reflecting the change in patient population from evaluable to randomized subjects requested by the health authority. Sentence about keeping 1 (or more) resection blocks at site has been deleted since detailed instructions are available in the central lab manual/flowchart as already mentioned in this section.
- Section 8.5.3: CT brain with contrast was added as an alternative to Brain MRI and use of contrast has been clarified.
- Section 8.5.4.2: Surgery instructions have been added as a guidance; The fact that surgery related information including safety-related will be collected in the eCRF has also been added.
- Section 9.1.1: EOT visit window has been updated to latest 21 days after the permanent discontinuation of study treatment but before the surgery for more flexibility with the patient's schedule and point of reference for safety follow-up visits has been corrected.
- Section 9.1.2: Withdrawal of consent section has been revised
- Section 9.2: Point of reference for safety follow-up visits has been corrected.
- Section 10.1.1: Dose reduction/increased was deleted since this is not allowed in the trial. In addition period for following up on AEs has been clearly defined.

[redacted]

- Section 10.1.1.1: 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.
- Section 10.1.4: Clarification added that, if pregnancy occurs while on study, the newborn will be followed for at least 12 months.
- Section 11.2: Change implemented to reflect the new protocol template version 3.0
- Section 12.4.1: Changed the patient population from evaluable to randomized subjects requested by the health authority.
- Section 12.4.2:
    - The target population was updated to all randomized patients who are histologically confirmed NSCLC stage IB-IIIA (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors.
    - The primary variable is clarified in details and the non-responder is specifically defined.
    - Study treatment was added as a new attribute for primary estimand.
    - Withdrawal of consent prior to surgery and lost to follow-up prior to surgery were removed from intercurrent events.
    - The intercurrent event of discontinuation of study treatment due to other reasons was further clarified as discontinuation of study treatment prior to surgery.
    - The strategy of handling intercurrent event discontinuation of study treatment prior to surgery was clarified to be treatment-policy strategy.
    - The strategy of handling intercurrent event of start of new antineoplastic therapy prior to surgery was updated to composite strategy.
    - The target MPR rate for the combination arm was updated to 45% which is a 25% absolute improvement to account for the change of analysis population from evaluable subjects to randomized subjects.
- Section 12.4.3: Updated to clarify the handling of unknown MPR status due to surgery not being performed (including lost to follow-up or withdrawal of study consent before surgery).
- Section 12.4.4: Updated to align with the changes made in Section 12.4.2. The intercurrent event of start of new antineoplastic therapy will be handled by treatment-policy strategy.
- Section 12.5.1: Updated to align with the changes made in Section 12.4.1 and 12.4.2 for the secondary objective of MPR including MPR per central review in pembrolizumab arm and MPR per local review in all three arms. Clarification was made on handling BOR of 'Unknown' per RECIST 1.1, and it is clarified that BOR is based on the assessment on the EOT visit.
- Section 12.6.2: TCR sequencing was deleted.

[redacted]

[redacted]

- Section 12.8.1: Changed the patient population from evaluable to randomized subjects requested by the health authority, and the target MPR rate for the combination arm was updated to 45% which is a 25% absolute improvement. Proof of efficacy and operating characteristic tables (Table 12-1 and Table 12-2) were updated accordingly, and the probability of erroneously declaring proof of efficacy is at most 2.1% while the probability of declaring proof of efficacy is at least 92.2% for MPR $\geq$ 55%.
- Section 15: New and missing references have been added.
- Section 16.1: Table 16-1 item 2 in General Instruction was updated to clarify that an interruption of pembrolizumab for 12 weeks is not allowed due to the length of the trial.
- Section 16.3.3.1: Pembrolizumab±canakinumab/matching placebo study treatment was deleted, because it was not applicable for the study.
- Section 16.3.4.2: End of treatment visit was changed to within 21 days of permanent discontinuation of study treatment but before the surgery.
- Section 16.4: Added NSCLC staging table according to AJCC 8th edition for clarification.

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

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.

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.

[redacted]

1 Introduction

1.1 Background

1.1.1 Disease background

Lung cancer is the most common invasive cancer and cause of cancer death worldwide. 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). NSCLC accounts for 85% of the lung cancer diagnoses and about 30% of subjects have surgically resectable disease at diagnosis (Molina et al 2008, Maeda et al 2010). Surgery is the treatment of choice for subjects with NSCLC stages I through IIIA. Five-year survival rates range from 50% for stage IA disease to 19% for stage IIIA disease (Goldstraw et al 2007), with most patients having postsurgical tumor relapse (Uramoto and Tanaka 2014). Despite apparently curative surgery, approximately 50% of stage IB and 70% of stage II NSCLC patients will relapse and eventually die of their disease. Given the current limited survival of patients with NSCLC, even in early stages of disease, new treatments options are needed. Neoadjuvant and adjuvant treatments are used to eradicate micrometastatic disease and minimize the risk of relapse.

1.1.2 Immunotherapy in NSCLC

Immunotherapy has recently shaped the treatment landscape of advanced NSCLC patients, both in the pre treated and treatment-naive setting. Monoclonal antibodies targeting PD-1 and Programmed death-ligand 1 (PD-L1) (nivolumab, durvalumab, pembrolizumab and atezolizumab) have 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 et al 2016, Antonia et al 2017, Langer et al 2016, Gandhi et al 2018, Borghaei et al 2015, Horn et al 2017, Rittmeyer et al 2017, Socinski et al 2018).

Nivolumab is approved in many countries for patients who have previously received chemotherapy for both squamous and non-squamous lung cancer based on two randomized phase 3 trials (Borghaei et al 2015, Brahmer et al 2015) that demonstrated superior overall survival (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 Progression Free Survival (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).

Pembrolizumab a monoclonal PD-1 inhibitor, 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). In the first-line setting, pembrolizumab was initially approved as monotherapy for NSCLC patients whose tumor has a PD-L1 expression ≥ 50% based on the results of KEYNOTE-024 (Reck et al 2016).

In addition, in Japan, pembrolizumab was approved as monotherapy in the first-line treatment of PD-L1-positive (Tumor Proportion Score (TPS) ≥ 1%) unresectable, advanced/recurrent

[redacted]

NSCLC (KEYNOTE-042), (Mok et al 2019). More recently, pembrolizumab was approved in combination with platinum-based doublet chemotherapy and pemetrexed in non-squamous NSCLC as first line treatment based on the results of KEYNOTE-189 (Gandhi et al 2018). Pembrolizumab was also approved in combination with carboplatin and either paclitaxel or nabpaclitaxel, as first-line treatment of patients with metastatic squamous NSCLC in the United States (US), based on the results of KEYNOTE-407 (Paz-Ares et al 2018).

Atezolizumab was approved for previously treated NSCLC with progression on or following a platinum-containing regimen (Rittmeyer et al 2017) regardless of the PD-L1 expression and of the histology and in the first line setting for non-squamous histology (with no Epidermal Growth Factor Receptor (EGFR) and ALK genomic tumor aberrations) in combination with bevacizumab, paclitaxel and carboplatin.

1.1.3 Neoadjuvant treatment and major pathological response as a surrogate endpoint

A meta-analysis based upon seven trials involving 988 patients suggested that neoadjuvant chemotherapy (platinum-based chemotherapy-cisplatin or carboplatin, combined with other agents) improved OS in patients with NSCLC when given preoperatively (five-year survival 20% versus 14% without neoadjuvant chemotherapy). This improvement in survival is similar to that observed in the meta-analyses of predominantly adjuvant chemotherapy (Burdette-Radoux and Muss 2006, Scagliotti et al 2012, Chuang et al 2017). The neoadjuvant setting offers the possibility for the identification of surrogate clinical and biological markers that may correlate with response to therapy and in some cases long-term outcome. In addition, preoperative therapy may be a useful platform for the development of new targeted therapies. Efficient strategies to evaluate promising agents in early phase development are essential for rapid progress in lung cancer treatment and prevention. Several studies have shown preoperative systemic therapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity and mortality (Depierre et al 2002, Gilligan et al 2007, Scagliotti et al 2012).

A comprehensive analysis of 192 patients with stage I-IV NSCLCs treated with neoadjuvant chemotherapy (mean of 3 treatment cycles; range 2-7 cycles) followed by complete surgical resection demonstrated an improved survival in those with 0-10% viable tumor compared to other groups. Among patients with NSCLC treated with neo-adjuvant chemotherapy, the hazard ratio for survival was 4.78 (95% confidence interval of 2.06–11.11) when comparing patients with > 70% viable tumor cells to those with ≤ 10% viable tumor cells (Pataer 2012). The correlation between MPR and survival outcomes remained significant when patients were stratified by stage supporting the relevance of MPR as an endpoint for clinical trials (Pataer 2012, Hellmann et al 2014). MPR, defined as ≤10% residual viable tumor, was demonstrated to positively correlate to disease free survival (DFS) and OS in patients treated with neo-adjuvant chemotherapy (Pataer 2012, Hellmann et al 2014) and thus used as a surrogate efficacy endpoint in some neo-adjuvant studies (Chaft et al 2013, Forde et al 2018, Shu et al 2018).

Chaft and colleagues performed a prospective trial investigating pathological response with the methods described by Pataer (Pataer 2012) and observed that among 50 patients with stage IB–

[redacted]

IIIA NSCLCs given neoadjuvant chemotherapy and bevacizumab, 22% patients had 10% or less viable tumor (MPR) (Chaft et al 2013).

Recent clinical studies demonstrated promising results of immunotherapy treatment in the neoadjuvant setting. PD-1 pathway blockade in patients with early stage lung cancer may have enhanced antitumor effects due to the greater fitness of host immunity and reduced tumor clonal heterogeneity (McGranahan et al 2016). Neoadjuvant immunotherapy is attractive, since the primary tumor may be leveraged as an antigen source for expansion and activation of tumor-specific T cells and systemic surveillance of micro-metastases.

A single arm study of nivolumab in 21 adults with untreated surgically resectable early (stage I, II, or IIIA) NSCLC given approximately for 4 weeks before the surgical resection (two preoperative doses of nivolumab Q2W), showed that MPR occurred in nine of the 20 resected tumors (45%; 95% CI, 23 to 68). Responses occurred in both PD-L1–positive (TPS ≥ 1%) and PD-L1–negative tumors; among 15 patients with evaluable PD-L1 expression, 3 and 2 patients had MPR, respectively. There was a significant correlation between the pathological response and the pretreatment tumor mutational burden. Patients who had a MPR were found to carry a significantly higher number of somatic sequence alterations than those without a MPR, with a mean (± SE) number of 311 ± 55 and 74 ± 60, respectively ($p = 0.01$ by exact Wilcoxon test) (Forde et al 2018). The tumor mutational burden was predictive of the pathological response to PD-1 blockade as evidenced by the treatment-induced expansion of mutation-associated and neoantigen-specific T-cell clones in peripheral blood. In addition, neoadjuvant treatment with nivolumab was associated with few side effects and did not delay surgery.

Neoadjuvant single arm study with atezolizumab in combination with carboplatin and nab-paclitaxel given for ~6 weeks before surgery also showed activity in this setting. Eleven of 14 patients successfully underwent resection and seven of 14 patients (50%) achieved MPR, including three with complete pathological responses (Shu et al 2018).

Another study in the neo-adjuvant setting is ongoing to evaluate atezolizumab as monotherapy in 180 patients with stage IB-IIIB resectable NSCLC. An initial pre-specified safety analysis showed that among 21 patients, 19 had MPR assessment and 4/19 (21%) had a MPR (Rusch et al 2018).

There are other ongoing studies with other immunotherapy drugs (such as pembrolizumab and durvalumab) in the neo-adjuvant setting.

1.1.4 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 2015).

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 pre-clinical data supports the role of IL-1β in several distinct steps in carcinogenesis.

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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 2007). IL-1β promotes tumor initiation by inducing the 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).

Supporting evidence published by Kaplanov and colleagues showed that IL-1β blockade in breast cancer models (by using either IL-1β-deficient mice or treatment with an anti-IL-1β antibody), resulted in anti-tumor activity which was associated with a decrease in macrophages and increase in dendritic cells as well as activated T-cells (Kaplanov et al 2018).

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 may also 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, Voronov et al 2003). The final step in carcinogenesis is metastasis. IL-1β plays 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 affect 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 affect 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 Immuno-Oncology (IO) agents such as anti-PD-(1) inhibitors used in combination.

Recent data confirming this hypothesis demonstrated synergistic anti-tumor activity of anti-IL-1β and anti-PD-1 combination treatments in a 4T1 breast cancer mouse model. In this model, while each of the monotherapy arms resulted in a decrease in tumor volume, the combination

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of both treatments completely abrogated the tumor growth, which was characterized by a significant increase in T-cells (Kaplanov et al 2018). In addition, 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.

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).

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

1.2.1 Canakinumab in NSCLC

Canakinumab (ACZ885) is a high affinity human anti-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. Novartis has investigated its use in the secondary prevention of major adverse cardiovascular events in the CANTOS trial (Canakinumab Anti-inflammatory Thrombosis Outcomes 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 canakinumab 50, 150 or 300 mg s.c. every three months for a median follow-up period of 3.8 years. The administration of canakinumab demonstrated a clinically and statistically significant effect in reducing the risk of Major Adverse Cardiovascular Events (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 (AE) was included as a pre-specified 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 2017a). The baseline concentrations of hs-CRP (median 6.0 mg/L vs 4.2 mg/L; $p<0.0001$) and IL-6 (3.2 vs 2.6 ng/L; $p<0{\cdot}0001$) were significantly higher for patients who subsequently diagnosed with lung cancer than those who were not diagnosed, respectively (Ridker et al 2017a). 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 2017a). 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 2017a). 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 a statistically significant reduction in risk (HR=0.49, 95% CI: 0.31-0.75, $p=0.0009$).

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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 2017a).

Circulating tumor deoxyribonucleic acid (ctDNA)

ctDNA was detected at baseline in 66% (44/67) of lung cancer patients from CANTOS, suggesting that these patients may have harbored undiagnosed lung cancer at the time of enrollment (Baum et al 2018). This included similar lung cancer driver mutations as reported in the literature (Chaudhuri et al 2017) and The Cancer Genome Atlas database. Additionally, baseline ctDNA positivity, as well as high baseline level of CRP and IL-6, trend with faster time to lung cancer occurrence. This trend was only observed with cytokines in the IL-1β/IL-6/CRP inflammation pathway. Amongst the inflammatory cytokines tested, IL-6 and CRP were downregulated by canakinumab, but no change was observed in other cytokines including IL-18 & TNF-α. These results suggest that the IL-1β/IL-6/CRP inflammation pathway may contribute more strongly than other inflammation pathways to lung cancer development, and canakinumab's effect may be mediated by delaying lung cancer progression (Baum et al 2018).

Safety

In the CANTOS study, during a median follow-up time of approximately 3.8 years, there were no meaningful differences between canakinumab treatment groups and placebo in the overall incidence of AEs, serious adverse events (SAEs), AEs leading to permanent discontinuation or to temporary interruption, or of SAEs leading to permanent discontinuation. The most frequently reported AEs were viral upper respiratory tract infections (12.5% and 13.9% for canakinumab 300mg and 150mg arms and 12.3% for placebo). The majority of infections resolved either spontaneously or with standard therapy. A slight increased risk of serious infections and of fatal infections/sepsis was observed in canakinumab versus placebo (SAEs of infections and infestations reported in 11.7%, 11.3% and 10.2% of subjects in canakinumab 300 mg, 150 mg and placebo arm, respectively). Rates of all grade AEs of neutropenia (2.0% and 1.4% for canakinumab 300 mg and 150 mg and 0.9% for placebo), thrombocytopenia (2.7% and 2.0% for canakinumab 300mg and 150mg and 1.6% for placebo) were low, even though also numerically higher in the canakinumab group compared with placebo. Decreased neutrophil and platelet counts, also reported for canakinumab, were not associated with an increased risk of infections or bleeding events. Overall, the safety and tolerability profile of canakinumab in the CANTOS study was consistent with the known safety profile in the approved indications, for which no specific target organ toxicity has been demonstrated (CANTOS CSR, Ridker et al 2017b).

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 2017a). This data along with the preclinical information that IL-1β supports tumorigenic inflammation provides the rationale to investigate the therapeutic role of canakinumab.

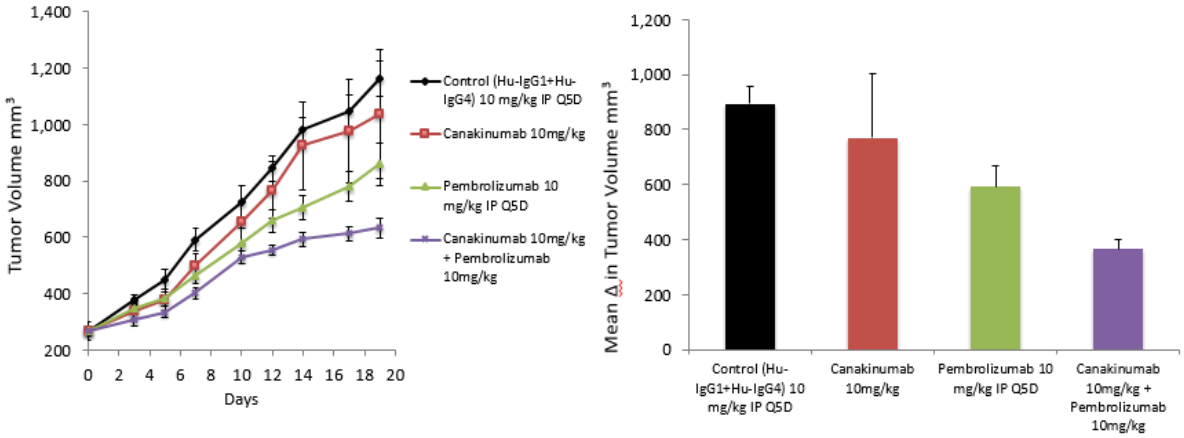
Pre-clinical data

Despite the well-known limitation of mouse models to study the effects of immunotherapy and anti-inflammation agents; preliminary mouse data showed that treatment with canakinumab single agent or combination with an anti-PD-1 inhibitor could lead to anti-tumor activity. First, in an EGFR mutant NSCLC (HCC827 cell line) humanized bone-liver-thymus (BLT) model,

[redacted]

anti-tumor activity was observed in 3 out of 5 mice after 3 weeks of treatment with canakinumab single agent or combination with pembrolizumab. Furthermore, 3 weeks combination treatment of canakinumab and pembrolizumab led to a significant tumor growth inhibition in the KRAS H358 NSCLC aggressive model (humanized BLT) compared to vehicle or single agent treatment. These treatments were well tolerated with no significant weight loss observed in treated mice (both studies were conducted at UCLA, (Jayaraman et al 2019)).

Figure 1-1 Activity of canakinumab, pembrolizumab and combination in H358 NSCLC cell line xenograft model



Hu-IgG: Humanized Immunoglobulin G

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 recognize and destroy the cancer cells. Pembrolizumab is already approved as first-line treatment of patients with metastatic non-squamous NSCLC in combination with chemotherapy, as a single agent for the first-line treatment of patients whose tumors have high PD-L1 expression (TPS ≥ 50%) and in the second line setting. Additionally, pembrolizumab is approved in the US in combination with chemotherapy as first-line treatment of patients with metastatic squamous NSCLC (Herbst et al 2016, Reck et al 2016, Langer et al 2016, Gandhi et al 2018, Paz-Ares et al 2018). See Section 1.1.2.

1.2.3 Canakinumab and PD-1 combination in NSCLC

The combination of canakinumab to a PD-1 inhibitor, such as pembrolizumab, is expected to build upon the activity of PD-L1/PD-1 inhibitors blocking the emerging resistance to PD-1 blockage through inhibition of the CRP/IL-1β axis and thereby resulting in a microenvironment more susceptible to anti-PD-(1) inhibitors. Correlation between the IL-1β pathway, CRP levels and PD-L1 expression has been observed and provides rationale for combining immune checkpoint inhibitors with an IL-1β pathway antagonist (Akamine et al 2018, Guo et al 2017).

No drug-drug interaction (DDI) is expected between pembrolizumab and canakinumab given both antibodies are eliminated by non-metabolism dependent pathway. The combination of

[redacted]

canakinumab and PDR001, a PD-1 inhibitor under development, has been evaluated in a Phase 1b dose finding study CPDR001X2103. This study has shown that canakinumab is safe to be combined with PDR001. No excess toxicity was observed with the combination canakinumab and PDR001, with the AE profile of the combination being representative of the individual AEs of each compound. The safety profile of PDR001 is similar to other PD-(L)1 inhibitors, thus combination of canakinumab and pembrolizumab is expected to be safe.

In addition, Study CACZ885U2301 (CANOPY-1), a Phase III randomized, double-blind study evaluating the combination of platinum-based doublet chemotherapy plus pembrolizumab with or without canakinumab in the first line setting in patients with both squamous and non-squamous (NSCLC) will include a Run-in phase to evaluate the safety of this combination.

Taken together, the role of IL-1β in carcinogenesis, the pre-clinical data, the ctDNA data and the reduction in lung cancer incidence and mortality in the CANTOS trial, support the hypothesis that canakinumab may provide tumor control/regression as single agent in the neo-adjuvant setting. In addition, the combination with pembrolizumab, leading to a more susceptible tumor micro-environment to PD-L1 inhibition, is expected to further enhance the benefit in this setting.

1.3 Purpose

The purpose of this randomized, open-label, phase II study is to evaluate the MPR rate of canakinumab given as a neoadjuvant treatment, either as single agent or in combination with pembrolizumab, in addition to evaluate the MPR of pembrolizumab as a single agent and the dynamic of the tumor microenvironment changes on treatment by comparing pre-, on- and post-treatment samples. MPR has been shown to positively correlate with OS and DFS in a study with patients receiving neo-adjuvant chemotherapy (Hellmann et al 2014)

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the MPR rate (≤10% of residual viable tumor cells) at the time of surgery in all subjects randomized to canakinumab alone and in combination with pembrolizumab arms based on central review	• MPR rate based on central review
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the prevalence and incidence of IG (ADA) of canakinumab and pembrolizumab	• ADA prevalence at baseline and ADA incidence on-treatment
• To assess ORR in randomized subjects treated with canakinumab or pembrolizumab as monotherapy and in combination (local review)	• Overall response rate based on local investigator assessment per RECIST 1.1
• To assess the PK of canakinumab and pembrolizumab as monotherapy and in combination	• Concentrations of canakinumab, pembrolizumab

[redacted]

Objective(s)	Endpoint(s)
• To assess surgical feasibility rate in each treatment arm based on randomized subjects	• Surgical feasibility rate
• To assess the MPR rate at the time of surgery in (a) all subjects randomized to pembrolizumab monotherapy arm based on central review, (b) all randomized subjects based on local review in each treatment arm, and (c) to estimate the difference in MPR and posterior probability of the difference in MPR ≥ 10% between subjects randomized to canakinumab + pembrolizumab combination and pembrolizumab alone based on central review	• (a) MPR based on central review (b) MPR based on local review (c) Difference in MPR rate based on central review
• To evaluate safety and tolerability of canakinumab and pembrolizumab as monotherapy or in combination	• Type, frequency and severity of AEs (Common Terminology Criteria for Adverse Events [CTCAE] v5.0), vital signs and laboratory abnormalities
• To assess the relationship between key blood or tissue based biomarkers and MPR	• MPR based on the levels of biomarkers (PD-L1, CD8, hs-CRP, hs-IL-6) assessed at baseline and on treatment
[redacted]	

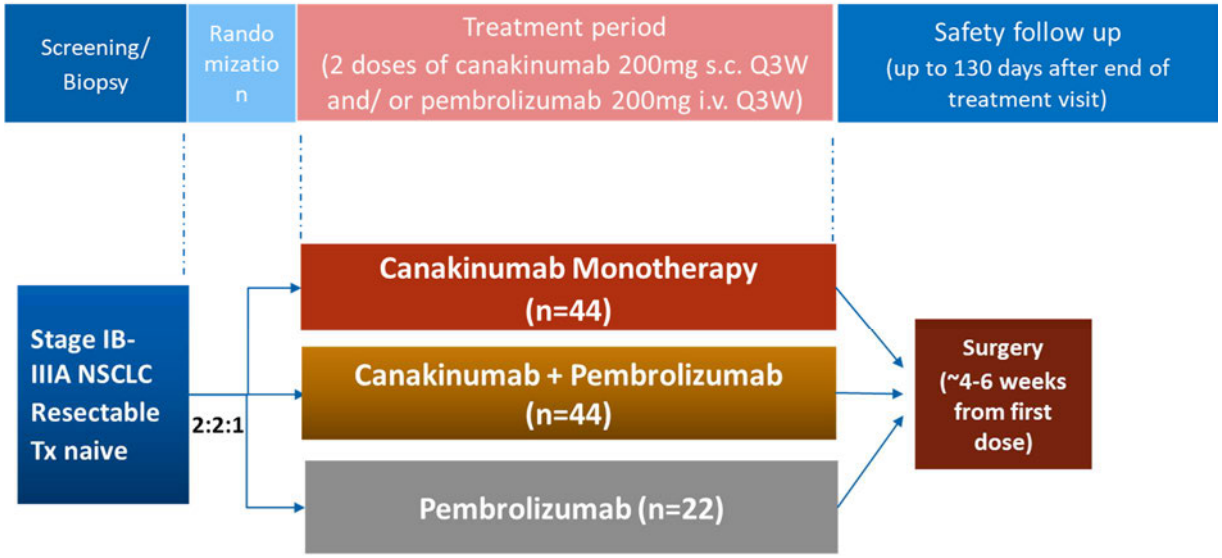
3 Study design

This is a phase II, randomized, open-label study evaluating efficacy and safety of canakinumab or pembrolizumab monotherapy or in combination as neoadjuvant treatment. Approximately

[redacted]

110 subjects will be randomized in a 2:2:1 ratio to one of the treatment arms (canakinumab alone or canakinumab in combination with pembrolizumab or pembrolizumab alone) and receive two doses of canakinumab (200mg s.c. Q3W) alone or in combination with pembrolizumab or two doses of pembrolizumab as single agent (200mg i.v. Q3W) (Figure 3-1). Randomization will be stratified by histology (squamous vs non-squamous).. Subjects will be treated for a maximum duration of 6 weeks (2 cycles) until surgery, progression, unacceptable toxicity or discontinuation from the study treatment for any other reason. Surgery must be performed between 4 to 6 weeks after the first dose of study treatment. Delay to the surgical procedure beyond 6 weeks is acceptable, but should be avoided. The primary endpoint is the MPR rate as assessed by the percentage of subjects with ≤ 10% residual viable cancer cells. The primary endpoint of MPR will be assessed centrally based on all randomized subjects, with local evaluation being a secondary endpoint. Primary analysis will be performed after all subjects have had surgical resection or have discontinued study treatment earlier due to any reason. Following the surgical procedure (or early discontinuation) subjects will not receive any further dose of study treatment. Subjects will enter in the safety follow-up period up to 130 days (i.e. canakinumab and pembrolizumab 5x half-life) after end of treatment visit.

Figure 3-1 Study design



4 Rationale

4.1 Rationale for study design

This randomized study will evaluate the effect of canakinumab and pembrolizumab given as monotherapy and in combination as neo-adjuvant treatment for subjects with early stages NSCLC. Randomization will be stratified by histology (squamous versus non-squamous). Rationale for study design features is described in Table 4-1.

[redacted]

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall design: three arms, parallel randomized design	This will reduce any treatment assignment bias and allow an assessment of the three treatment arms in the same setting and similar patient population.
Randomization stratification factors: • Histology (squamous vs. non-squamous)	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, Paz-Ares et al 2018, Paesmans 2012). Therefore randomization is stratified based on disease histology.
Open-label study	Treatment blinding was not considered necessary since the investigators will have no influence on the primary outcome of the study. However, the primary endpoint will be evaluated based on surgically resected sample by independent pathologists who will be blinded to the treatment arms.
Duration of study treatment: 4-6 weeks	The duration of treatment will be short and flexible (4-6 weeks). The objective is to allow sites to have some flexibility to schedule the surgical procedure based on their local practice and at the same time avoid delays. Additionally, it has been shown that checkpoint inhibitors, such as nivolumab, led to major pathological responses following a 4 week treatment period (Forde et al 2018) and canakinumab leads to early (~7 days) and sustained reduction of C-reactive protein (CRP) (Alten et al 2008) in addition IL-6 and IL-1RA (Lachmann et al 2007), thus 4-6 weeks is considered enough to observe the treatment effect
Unbalanced randomization: 2:2:1	The primary endpoint is to assess the MPR rate in canakinumab alone and in combination with pembrolizumab. The pembrolizumab arm is added to estimate the background MPR rate of pembrolizumab in order to assess the contribution of canakinumab when combined with pembrolizumab, thus the randomization (2:2:1) will prioritize the two canakinumab arms, and less patients will be randomized to the pembrolizumab monotherapy arm.

4.2 Rationale for dose/regimen and duration of treatment

In this phase II, randomized, open-label study, canakinumab dose will be 200mg Q3W, which is the dosing regimen selected for the development program in NSCLC. This dosing regimen is chosen on the basis of the PK and PD properties of canakinumab, the observed safety,

[redacted]

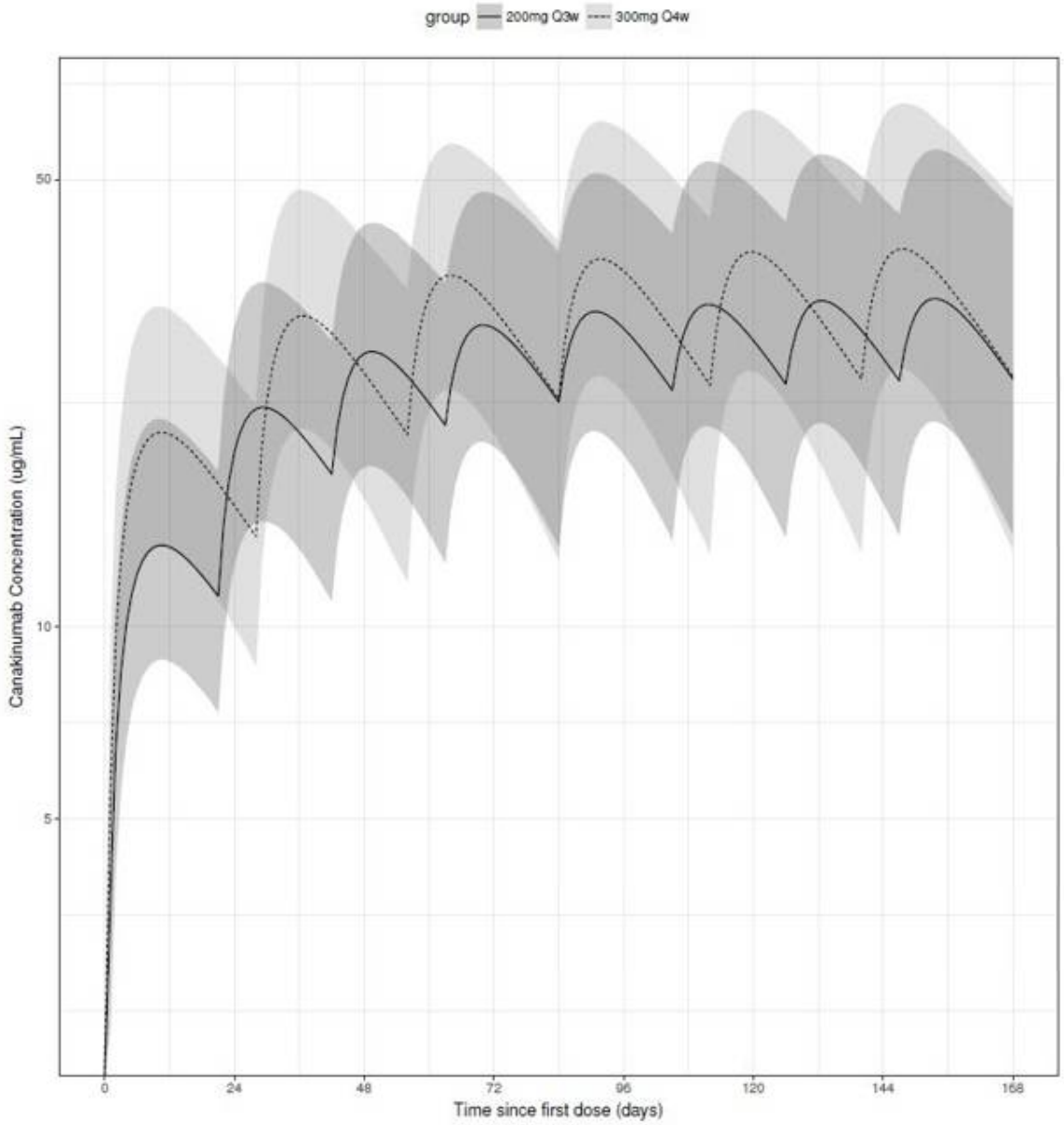
biomarker and efficacy data from the CANTOS study, and the safety data from completed and ongoing canakinumab studies.

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 s.c. 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.

[redacted]

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

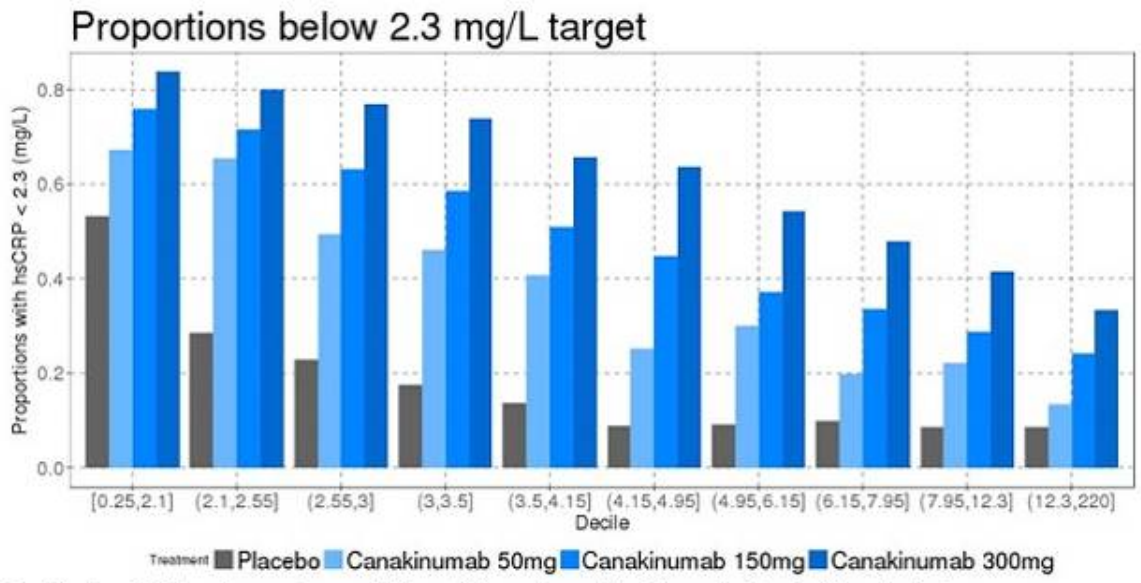
CANTOS study evaluated whether IL-1β inhibition might alter cancer occurrence and mortality as there is a strong inflammatory component to certain cancers, especially lung cancer. The results show that canakinumab, as compared to placebo, was associated with dose-dependent risk reductions in lung cancer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

[redacted]

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 2017a). 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 lung 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 2017a) 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 below 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

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 [IB]). There were no meaningful differences between any of the canakinumab treatment groups and placebo in the overall incidence of AEs 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.

Pembrolizumab dose of 200 mg Q3W is the approved dose for subjects with advanced NSCLC, either as monotherapy or in combination with chemotherapy.

4.2.4 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 8.4 for further details). The full dose of pembrolizumab (200 mg Q3W) is expected to be administered as no additive toxicity is anticipated from this combination.

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

This is a proof-of-concept study to evaluate the effect of canakinumab and pembrolizumab alone and in combination in the neo-adjuvant setting. As described above (Section 1.1.3), chemotherapy as neo-adjuvant therapy has shown limited benefit compared to surgery alone. There is an unmet medical need in this setting. With the recent approval of immunotherapy compounds in advanced/metastatic NSCLC, study results have emerged with immunotherapy compounds, such as nivolumab and atezolizumab, in the neo-adjuvant treatment. These studies have shown that these compounds can lead to MPR in the neoadjuvant setting. Pembrolizumab is also approved in the first line treatment as monotherapy (for patients with high PD-L1- TPS > 50%; and with TPS>1% in Japan only) and in combination with platinum-based doublet chemotherapy for patients with advanced NSCLC and is being studied as neo-adjuvant treatment. Pembrolizumab is expected to provide similar benefit as nivolumab in the neo-adjuvant setting. Canakinumab, as monotherapy in CANTOS trial, has led to a reduction in hs-CRP, potential reduction in the frequency of allelic mutations of the circulating tumor DNA cells and reduction in the incidence and in the mortality due to lung cancer. Canakinumab is also being studied in different settings in lung cancer (adjuvant, first and second lines) as monotherapy (adjuvant), in combination with pembrolizumab and chemotherapy (first line) and in combination with docetaxel (second line). Considering that canakinumab is very well-tolerated with low frequency of AEs reported, the benefit of pembrolizumab treatment in NSCLC patients, the results showing MPR with PD-L1 blockage and the unmet medical need in the neo-adjuvant setting, canakinumab and pembrolizumab were selected as treatment options in monotherapy and in combination in this study.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable

4.5 Risks and benefits

This phase 2 randomized study will evaluate the effect of canakinumab and pembrolizumab alone and in combination in patients with NSCLC in the neo-adjuvant setting. Several studies have shown preoperative systemic therapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity and mortality (Depierre et al 2002, Gilligan et al 2007, Scagliotti et al 2012). However, as described above (Section 4.3), chemotherapy in the neo-adjuvant setting has shown limited benefit compared to surgery alone. Thus, there is still an unmet medical need in this setting. With the recent approval of immunotherapy compounds in advanced/metastatic NSCLC, study results have emerged with nivolumab and atezolizumab in the neo-adjuvant setting showing that these drugs can lead

[redacted]

to MPR, which have been shown to positively correlate to long-term outcome such as DFS and OS. Pembrolizumab is expected to provide similar benefit as nivolumab in the neo-adjuvant setting, based on the benefits already shown in different settings in patients with NSCLC.

Canakinumab, as monotherapy in CANTOS trial, has led to a reduction in hs-CRP with a potential reduction in the frequency of allelic mutations of the ctDNA cells and reduction in the incidence and in the mortality due to lung cancer. Canakinumab is also being studied in different settings in lung cancer (adjuvant, first and second line) as monotherapy (adjuvant), in combination with pembrolizumab and chemotherapy (first line) and in combination with docetaxel (second line). Canakinumab combined with pembrolizumab is expected to lead to the modulation of the tumor micro environment such that the tumor is rendered more susceptible to PD-1 inhibition.

In this study, the neo-adjuvant treatment with canakinumab and pembrolizumab alone and in combination will be of short duration (4-6 weeks) and is expected to be well-tolerated and to lead to MPRs. Between NSCLC diagnosis and the date of the surgery, there is usually a window of time during which the standard preoperative evaluation is performed. Therefore, no delays in the surgical procedure is expected. Please note that this is dependent upon local practice.

In the CANTOS study, with median follow-up of 3.8 years, types and incidence of most infections (all grades included) were generally comparable across the treatment groups (51.5% all dose combined vs 50.4% placebo).

Based on the CANTOS study (n= 10,066 in the safety set), the proportion of patients with AEs of neutropenia (2.0% in the 300 mg arm, 1.4% in the 150 mg arm, 1.1% in the 50 mg arm and 0.9% in the placebo arm); thrombocytopenia (2.7% in the 300 mg arm, 2.0% in the 150 mg arm, 2.0% in the 50 mg arm and 1.6% in the placebo arm) and events of sepsis (2.2% in the 300 mg arm, 2.1% in the 150 mg arm, 1.8% in the 50 mg arm and 1.3% in the placebo arm) was low.

In addition, a low, but significantly higher risk of fatal events attributed to infection or sepsis per 100 person-years was noted in the three canakinumab dose groups combined than in the placebo group (incidence rate 0.31 vs 0.18; P=0·023). Time to event analysis on IAC confirmed-infection events showed that a considerably low proportion of patients presented with the first event of infection within the 3 months of the study treatment across canakinumab arms (1.1% in canakinumab 300 mg arm). Even though the frequency of infection with canakinumab is low, specifically if considering first 3 months of treatment, complete blood counts with differentials will be followed carefully and urinalyses will be routinely performed on study visits. Subjects are to notify the investigator 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].

KEYNOTE-024 was a phase III randomized trial of pembrolizumab as first line monotherapy vs chemotherapy in patients with NSCLC with PD-L1 expression ≥ 50%. In the pembrolizumab group, the most common (> 10%) treatment-related AEs were diarrhea (14.3%), fatigue (10.4%) and pyrexia (10.4%). The most common (> 5%) immune-mediated AEs in patients receiving pembrolizumab were hypothyroidism (9.1%), pneumonitis (5.8%) and hyperthyroidism (7.8%) (Reck et al 2016). These toxicities are not expected to overlap with canakinumab safety profile, which is also supported by the observations from Study CPDR001X2103, described in Section 4.2.

[redacted]

Even though both canakinumab and pembrolizumab are generally well-tolerated, appropriate eligibility criteria, specific dose modification and stopping rules are included in this protocol to ensure subjects' safety. Recommended guidelines for prophylactic or supportive management of study-drug induced AEs 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.

Women of child-bearing potential 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 (CT, magnetic resonance, PET-scan or X-rays) will be used in this study to assess response of tumors to administered treatments. There are two tumor assessments planned in the study, one tumor assessment at screening/baseline and one within 7 days prior surgery, for more details please refer to Section 8.5.3. Tumor assessments required by the trial allow for MRI and CT; the ability to use MRI instead of CT for the brain and abdomen decreases the radiation exposure. Only in the chest CT is 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.

NSCLC is an aggressive disease, even in early stages, with a high chance of recurrence. Given that canakinumab and pembrolizumab are expected to lead to MPRs (and potentially lead to a prolonged disease-free time), are well-tolerated and subjects will be closely monitored for safety, the potential benefits outweighs the risks of the short treatment duration with these compounds, favoring subjects to participate in the study.

5 Population

The study population will include approximately 110 adult subjects with histologically confirmed stage IB-IIIA NSCLC planned for surgery in approximately 4-6 weeks. 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. There will be no replacement of subjects who discontinued the study treatment for any reason.

5.1 Inclusion criteria

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

1. Subjects must provide written informed consent prior to any screening procedures being performed.
2. Male and female patients ≥ 18 years of age from the date of birth.
3. Histologically confirmed NSCLC stage IB-IIIA (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors (please refer to Appendix 16.4).
4. Subject must be eligible for surgery and with a planned surgical resection in approximately 4-6 weeks (after the first dose of study treatment).

[redacted]

5. A mandatory newly obtained tissue biopsy from primary site is required for study enrollment. An archival biopsy is also acceptable if obtained up to 5 months before first day of study treatment and if the subject did not go through antineoplastic systemic therapies between biopsy collection date and beginning of study treatment.

   Note: Aspirates will not be accepted.
6. Subjects must have adequate organ function including the following laboratory values at the screening visit:
   1. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
   2. Platelets $\geq 100 \times 10^9$/L
   3. Hemoglobin (Hgb) > 9 g/dL
   4. Creatinine clearance greater than 45 mL/min by calculation using Cockcroft-Gault formula
   5. Total bilirubin (TBIL) $\leq$ 1.5 x upper limit of normal (ULN)
   6. Aspartate transaminase (AST) $\leq$ 3 x ULN
   7. Alanine transaminase (ALT) $\leq$ 3 x ULN
   8. Serum amylase $\leq$ 2 x ULN or pancreatic amylase $\leq$ 1.5 x ULN
7. Subject must have adequate cardiovacular and respiratory function to be submitted to surgical procedure as assessed per local clinical practice.
8. ECOG PS of 0 or 1.
9. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.2 Exclusion criteria

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

1. Subjects with unresectable or metastatic disease. All patients should have brain imaging (either MRI brain or CT brain with contrast) prior to enrollment to exclude brain metastasis.
2. History of severe hypersensitivity reactions to monoclonal antibodies, which in the opinion of the investigator may pose an increased risk of serious infusion reaction.
3. Presence or history of a malignant disease that has been diagnosed and/or required therapy within the past 3 years. 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.
4. Subjects who received prior systemic therapy (including chemotherapy, other anti-cancer therapies and any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways) in the past 3 years before screening.
5. 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.
6. Uncontrolled diabetes as defined per the investigator.
7. History of (non-infectious) pneumonitis that required steroids or current pneumonitis.

[redacted]

8. Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as:
   a. Unstable angina or myocardial infarction within 6 months prior to screening
   b. History of documented congestive heart failure (CHF) (New York Heart Association functional classification III-IV)
   c. Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to randomization
   d. Ventricular arrhythmias
   e. Supraventricular and nodal arrhythmias not controlled with medication
   f. Other cardiac arrhythmia not controlled with medication
9. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior to randomization or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥1 week after the procedure.
10. 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 presence of TB (active or latent) is established then treatment for TB must have been completed according to locally approved country guidelines prior to screening for the study.
    - 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. 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
    - Subject receiving any biologic drugs targeting the immune system (for example, TNFα blockers, anakinra, rituximab, abatacept, or tocilizumab).
    - Current treatment with any immune modulating agent in doses with systemic effects e.g.:
      - Current systemic glucocorticoid therapy except for daily glucocorticoid-replacement for conditions such as adrenal or pituitary insufficiency and topical, inhaled or local steroid use in doses that are not considered to cause systemic effects are permitted
      - Prednisone > 20 mg (or equivalent) daily for > 14 days;
      - Prednisone > 5 mg and ≤ 20 mg (or equivalent) daily for > 30 days;
      - Equivalent dose of methotrexate > 15 mg weekly.
11. Live vaccination within 3 months prior to randomization.

[redacted]

12. Subjects who have received an investigational drug or device within 5 half-lives prior to randomization or those who are expected to participate in any other investigational drug or device during the conduct of the study.
13. 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 human chorionic gonadotropin (hCG) laboratory test.
14. 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 for 4 months after stopping study treatment.
    - 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.
15. 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).

6 Treatment

6.1 Study treatment

In this study, the "study treatment" refers to both canakinumab and pembrolizumab study drugs administered either as monotherapy or in combination of study drugs: canakinumab plus pembrolizumab. The term "investigational drug" refers to the Novartis study drug, canakinumab (ACZ885).

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

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
Pembrolizumab[a]	Concentrate for solution for i.v. infusion in vial Lyophilized powder for solution for i.v. infusion in vial	100 mg/4 mL (25 mg/mL) 50 mg	200 mg	Q3W

[a] Either concentrate solution or lyophilized powder formulations of pembrolizumab can be used if approved by local country regulations.
For preparation and dispensation please refer to Section 6.7

6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

Subjects will be randomized at cycle 1 Day 1 visit to one of the following 3 treatment arms/groups (canakinumab alone or canakinumab in combination with pembrolizumab or pembrolizumab alone) in a ratio of 2:2:1.

For preparation and dispensation please refer to Section 6.7.

6.1.4 Guidelines for continuation of treatment

Guidelines for management of toxicities and dose modification instructions please refer to Section 6.5.

Continuation of treatment beyond the 2 cycles prior and after the surgery is not permitted.

[redacted]

6.1.5 Treatment duration

Subjects will receive a maximum of two cycles of treatment (Q3 weeks). After the second study drug administration (Cycle 2), study treatment will be completed and subject will undergo the surgical procedure (4 to ~6 weeks after the first study drug administration). Study treatment can discontinue earlier in case of disease progression radiologically documented by investigator assessment, unacceptable toxicity that precludes further treatment, at the discretion of the investigator, subject withdrawal of consent, pregnancy, lost to follow-up, or death. No crossover treatment between the arms is allowed.

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. Granulocyte Colony-Stimulating Factor [G-CSF], anti-emetics, anti-diarrhea) is permitted except when specifically prohibited (Section 6.2.2). For pembrolizumab, 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 electronic case report form (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.

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 randomizing a subject or allowing a new medication to be started. If the subject is already randomized, contact Novartis to determine if the subject should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

6.2.1.1.1 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 .*Note: For Drug-Drug interaction (DDI) potential, please refer to Section 1.2.3* .

[redacted]

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). This is clinically relevant for CYP450 substrates with a narrow therapeutic index. Caution should be exercised when administering these agents (see Table 6-2) 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.

6.2.2 Prohibited medication

6.2.2.1 Prohibited concomitant medications for canakinumab

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.

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., TNFα 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
- Live vaccines within 90 days of study treatment and after initiation of study treatment. Subjects must be discontinued from study treatment 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 surgery.

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

6.3 Subject numbering, treatment assignment, randomization

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 enrolled for 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.

[redacted]

Upon signing the informed consent form (ICF), the subject is assigned to the next sequential Subject No. available to the investigator through the Clinical Data Management System interface.

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 or randomized or start treatment for any reason, the reason will be entered into the appropriate eCRF page.

6.3.2 Treatment assignment, randomization

At visit C1D1, prior to dosing, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by histology (squamous vs non-squamous). Subjects with adenosquamous histology can be stratified as squamous or non-squamous based on the predominant histology.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons on site performing the assessments, and Novartis global and local trial teams. However, treatment will be blinded to the independant pathologists (evaluating the primary endpoint based on surgical resected sample) from time to randomization until database lock.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted.

6.5.1 Dose modifications

For subjects who do not tolerate the protocol-specified dosing schedule the following principles must be followed:

- For both canakinumab and pembrolizumab dose reductions are not permitted.

[redacted]

- Increase in the canakinumab dosing interval to Q6W is not applicable due to the short duration of the study.
- Canakinumab dose interuption for a maximum of 1 week is allowed as per Table 6-2.
- Pembrolizumab will follow locally approved labels (if pembrolizumab is not yet approved in your country, refer to Section 16.1) and local clinical practice.

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

6.5.1.1 Guidelines for mandatory dose modifications for canakinumab

Mandatory dose interruption or discontinuation of canakinumab in the management of adverse reactions are summarized in Table 6-2. Clinical judgment of the treating physician should guide the management plan of each subject based on individual benefit/risk assessment. Canakinumab must be discontinued as listed for events in Table 6-2. If a subject experiences more than one toxicity and there are conflicting recommendations between canakinumab and pembrolizumab dose modification, the most conservative dose modification should be followed.

In the combination arm, if one of the study drugs (canakinumab or pembrolizumab) is permanently discontinued because of unacceptable toxicity, per the investigator discretion, the other study drug (canakinumab or pembrolizumab) can continue alone in Cycle 2.

Table 6-2 Criteria for mandatory dose interruption and re-initiation for canakinumab due to adverse reactions

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule interruption and re-initiation for canakinumab[g]**
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 canakinumab
Grade 3	Interrupt canakinumab until resolved to ≤ Grade 2, then: • If resolved in ≤ 7 days administer the second dose of canakinumab • If resolved in > 7 days discontinue canakinumab, due to the short study duration
Grade 4	Permanently discontinue canakinumab
Exceptions to the above general guidance[e]	
Neutropenia (ANC)	
Grade 2 (ANC < 1500 - 1000/mm^3)	Interrupt canakinumab until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days discontinue canakinumab, due to the short study duration.
Grade 3 (ANC < 1000 - 500/mm^3)/ Grade 4 (ANC < 500/mm^3)	Permanently discontinue canakinumab

[redacted]

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule interruption and re-initiation for canakinumab[g]**
Febrile neutropenia	
• Grade 4	Permanently discontinue canakinumab
Thrombocytopenia	
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Interrupt canakinumab until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days, permanently discontinue canakinumab
Serum creatinine	
Grade 3 (>3.0 x baseline; >3.0 - 6.0 x ULN)	Interrupt canakinumab until resolved to ≤ Grade 2 or baseline, then re-start at the same dose. • If resolved within 7 days, administer the second dose of canakinumab • If resolved in > 7 days discontinue canakinumab, due to the short study duration
Isolated total bilirubin elevation[a*]	
Grade 1 (Any elevation) > ULN – 1.5 x ULN	Fractionate bilirubin, evaluate for cholestatic liver injury (alkaline phosphatase (ALP)) or alternative causes of bilirubin elevation (e.g. disease progression [imaging]). Treat alternative causes according to local institutional guidelines. Maintain canakinumab
Grade 2 > 1.5 - 3.0 x ULN	Maintain canakinumab. Repeat Liver function tests (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[b]	Interrupt canakinumab. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline. • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days, permanently discontinue canakinumab
Grade 4 > 10.0 x ULN[b]	see footnote* - otherwise discontinue canakinumab
Isolated AST or ALT elevation[a]	
With normal baseline AST/ALT:	
Grade 1 > ULN - 3.0 x ULN	Maintain canakinumab
Grade 2> 3.0 - 5.0 x ULN	Maintain canakinumab Repeat LFTs within 48-72 h; if still abnormal then monitor LFTs at least weekly, until resolved to ≤ 3.0 x ULN[c]

[redacted]

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule interruption and re-initiation for canakinumab[g]**
Grade 3: AST or ALT > 5.0 - 10.0 x ULN	Interrupt canakinumab. Repeat LFTs within 48-72 h; monitor LFTs at least weekly, until resolved to ≤ 3.0 x ULN. Then: • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days, discontinue canakinumab, due to the short study duration[c]
Grade 3: AST or ALT > 10.0 - 20.0x ULN	Permanently discontinue canakinumab. Repeat LFTs within 48-72 h; monitor LFTs at least weekly until resolved to ≤ baseline.
Grade 4: AST or ALT > 20.0 x ULN	Permanently discontinue canakinumab. 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 ULN):	
ALT/AST > 2.0 x baseline AND > 5.0 x ULN	Interrupt canakinumab. Repeat LFTs within 48-72 hours, then monitor LFTs weekly until recovery to baseline. • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days, discontinue canakinumab, due to the short study duration
ALT/AST > 3.0 x baseline AND >10 x ULN	Permanently discontinued canakinumab. Repeat LFTs within 48-72 hours, then monitor weekly until resolved to baseline.
AST/ALT increase associated with concomitant total bilirubin increase[a]	
With normal baseline LFTs:	
AST or ALT >3.0 x ULN associated with concomitant TBIL >2.0 x ULN without evidence of cholestasis[c] (unless Gilbert syndrome)	Interrupt canakinumab. Assess if case is true Drug Induced Liver Injury (DILI).* **If DILI confirmed** - Permanently discontinue canakinumab **If Not DILI** – interrupt canakinumab. Treat the identified cause according to institutional guidelines. Repeat LFTs within 48-72 hours, then monitor weekly, until enzyme levels resolve to ≤ Grade 1 or Baseline[d] Refer to Section 6.5.2.1 for additional follow-up of potential DILI cases as applicable
With abnormal baseline LFTs:	

[redacted]

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule interruption and re-initiation for canakinumab[g]**
ALT or AST >3 x baseline OR ALT or AST >8 x ULN (whichever is lower) combined with TBIL >2.0 x ULN	After recovery, re-administration of the second dose of canakinumab could be considered only if Investigator assesses benefit to outweigh the risk. Any decision regarding re-administration of canakinumab and dose regimen, should be discussed with the Novartis medical and safety team. Refer to Section 6.5.2.1 for additional follow-up evaluations as applicable
Pancreatitis[f]	
Grade 3	Interrupt canakinumab until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days, discontinue canakinumab
Hypertension	
Grade 3	Interrupt canakinumab until resolved to ≤ Grade 1, then: • If resolved in ≤ 7 days, administer the second dose of canakinumab • If resolved in > 7 days, discontinue canakinumab
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	
Tuberculosis or reactivation of hepatitis	
• Permanently discontinue canakinumab	
Asymptomatic laboratory abnormalities- Provide supportive care and replacement therapy	
• If clinically significant, follow general guidelines	
LFTs – Liver Function Tests [a] Refer to protocol Section 6.5.2.1 for monitoring of liver toxicity [b] If TBIL > 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 canakinumab at the discretion of the investigator [c] The subject should be monitored biweekly (including LFTs), or more frequently if clinically indicated, until TBIL have resolved to baseline or stabilization over 4 weeks [d] Repeat within 48 hours then at least weekly until AST, ALT, or bilirubin have resolved to baseline or stabilization over 4 weeks [e] If relatedness to canakinumab can be excluded with certainty and there is no risk for the patient, the dose interruption for canakinumab is not mandatory [f]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	

[redacted]

Worst toxicity (CTCAE v5.0) during a cycle of therapy	**Mandatory dose schedule interruption and re-initiation for canakinumab[g]**
[g] If AE is resolved prior to planned C2D1 dose interruption is not applicable. If AE is not resolved prior to planned C2D1, please follow dose interruption recommendation. * 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, Gamma-glutamyl-transferase (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.	

6.5.2 Follow-up for toxicities

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

DILI Diagnosis

Subjects with transaminases increase combined with TBIL increase may be indicative of potentially severe DILI, and should be considered as clinically important events and should be assessed appropriately to establish 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 6-2, Section 6.5.1.1); subjects meeting any of the following criteria will require further follow-up 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 > 3.0 x baseline or 8.0 x ULN, whichever is lower combined with (TBIL > 2.0 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, TBIL, direct and indirect bilirubin, ALP (fractionated if ALP 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 LFTs elevations are caused by cholestasis (defined as: ALP elevation > 2.0 x ULN with R value < 2 in subjects without bone metastasis, or elevation of ALP liver fraction in subjects with bone metastasis).

[redacted]

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

Table 6-3 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 6-3 Specific clinical and diagnostic assessments

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-Hepatitis A Virus (HAV); HBsAg, IgM & IgG anti-HBc, Hepatitis B Virus (HBV) DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Epstein-Barr Virus (EBV) infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• Antinuclear Antibody (ANA) & Anti-Smooth Muscle Antibody (ASMA) titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, Mean Corpuscular Volume (MCV), Carbohydrate Deficient-transferrin (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)	• Caeruloplasmin
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, Thyroid-Stimulating Hormone (TSH); Cardiovascular Disease (CVD) / Ischemic hepatitis – Electrocardiogram (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.

DILI Management

In the absence of cholestasis, these subjects should be immediately discontinued from study drug treatment, and repeat 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:

[redacted]

- 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.
- 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.

6.5.2.2 Follow up for infections

Infections are the most common AE 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, on Day 1 of every cycle, End of Treatment (EOT) and at safety follow-up visits 1, 3 and 5.

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) and/or registration of the other study drug (pembrolizumab) dispensed to the subjects.

[redacted]

The date and time of all study treatment administrations during the study and any deviations from the protocol treatment schedule will be captured on the appropriate drug accountability log.

Exposure to the study treatment will be based on the number of injections and/or infusions administered. Compliance with the study treatment will be assessed by the field monitor at each visit using vial counts and information provided by the pharmacist or by the investigator. All study treatment dispensed must be recorded in the drug accountability log.

6.6.2 Emergency breaking of assigned treatment code

Not Applicable

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

Canakinumab (investigational drug):

Each study site will be supplied by Novartis with the investigational drug in packaging of identical appearance per product volume. Canakinumab is provided in pre-filled syringes, ready for use and no preparation is needed. For more details, please refer to Section 6.1. For further information on Canakinumab injection, please refer to instruction for use canakinumab manual.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

Pembrolizumab (other study drug)**:**

Pembrolizumab will be supplied locally as commercially available by the site pharmacy or by Novartis, if so, the drug 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 treatment 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 treatment must be stored according to the instructions specified on the labels and in the IB. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

[redacted]

Medication labels will be in the local language and comply with the legal requirements of each country. 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 treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely 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 all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not Applicable

6.7.2 Instruction for prescribing and taking study treatment

Administration of study treatment

Canakinumab (one syringe of 1 mL and one syringe of 0.5mL) will be administered by study site personnel via s.c. injections once every 3 weeks.

Pembrolizumab will be administered by study site personnel via i.v. infusion once every 3 weeks as per locally approved label and local practice.

For combination arm, study drugs should be administered sequentially, on the same day (canakinumab 200mg s.c injection then 30 minutes later pembrolizumab 200 mg i.v. infusion during 30 minutes)

The infusion time reported for pembrolizumab (30 min: -5 min/+10 min) is suggestion only. The locally approved label and local practice is to be followed.

Table 6-4 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
Canakinumab 200mg	200mg (1 X 150mg/1mL syring and 1x 50mg/0.5mL syringe)	C1D1 (Day 1) and C2D1 (Day 22)
Pembrolizumab 200mg	200mg (refer to Table 6-1)	C1D1 (Day 1) and C2D1 (Day 22)

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/Independent 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 ICF that complies with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use' (ICH) Good Clinical Practice (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 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.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
- Pregnancy Outcomes Reporting Consent for female subjects

Women of child bearing potential 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.

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

Subjects might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience (please refer to Section 8.5.4.1).

8 Visit schedule and assessments

The assessment schedule Table 8-2 lists all of the assessments and indicates with an "X", the visits when they are performed. Note: when the assessment is indicated with an "S", this will be documented in the subject source medical record only. All data obtained from these assessments (indicated with an "X" and "S") 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 dose modification criteria in Section 6.5.1 and the locally approved label and local practice for pembrolizumab. During

[redacted]

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.

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

Visit name	Window
Screening	-1 to -28 Days before Cycle 1 Day 1
All assessments including C1D1, during the treatment period (except tumor assessments)	± 3 Days (-3 days for Cycle 1 Day 1)
Canakinumab injection (if applicable)	± 3 Days
Pembrolizumab infusion (if applicable)	± 3 Days
PK/IG/PD sampling	Refer to tables in Section 8.5.1
26, 52, 78 and 104 day safety follow-up visits	± 7 Days
130-day safety follow-up visit	+ 14 Days
EOT	≤ 21 Days after permanent discontinuation of study treatment, but before the surgery
EOT biomarker sampling	At time of surgery if possible, if not within 4 days prior to surgery

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-2) or as close to the designated day/time as possible. 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 and safety follow-up visits will be performed. At this final visit, the AE and concomitant medications should be recorded on the case report form (CRF).

[redacted]

Table 8-2 Assessment Schedule

Period	Screening	Treatment		EOT		Safety Follow-up					EOS
Cycle		Cycle 1	Cycle 2								
Visit Name	Screening	Treatment C1D1	Treatment C2D1	EOT	Surgery	Safety Follow-up 1	Safety Follow-up 2	Safety Follow-up 3	Safety Follow-up 4	Safety Follow-up 5	EOS
Days	-28 to -1	1	22	When applicable[6]	4 to 6 weeks	From EOT: 26	From EOT: 52	From EOT: 78	From EOT: 104	From EOT: 130	-
Informed consent	X										
IRT Screening (after ICF signature)	X										
Demography	X										
Inclusion / Exclusion criteria	X										
Medical history/current medical conditions	X										
Smoking history	X										
Diagnosis, stage and grade of cancer	X										
Archival or newly obtained tumor sample[1]	X										
Histopathology assessment, (squamous or non-squamous)	X										
Hepatitis screen	X	If clinically indicated									
Determination of tuberculosis status	S										

[redacted]

Period	Screening	Treatment		EOT		Safety Follow-up					EOS
Cycle		Cycle 1	Cycle 2								
Visit Name	Screening	Treatment C1D1	Treatment C2D1	EOT	Surgery	Safety Follow-up 1	Safety Follow-up 2	Safety Follow-up 3	Safety Follow-up 4	Safety Follow-up 5	EOS
Days	-28 to -1	1	22	When applicable[6]	4 to 6 weeks	From EOT: 26	From EOT: 52	From EOT: 78	From EOT: 104	From EOT: 130	-
HIV history (HIV testing where locally required)	S										
Total T3, T4 and TSH	X	X	X	X		X					
Eligibility checklist (Within IRT randomization)		X									
Physical Examination	S	S	S	S		S		S		S	
ECOG Performance status	X	X	X	X		X		X		X	
Vital Signs	X	X	X	X		X		X		X	
Body Weight	X	X	X	X							
Body Height	X										
Electrocardiogram (ECG)		pre-dose	If clinically indicated								
Hematology blood sample	X	X	X	X		X		X		X	
Chemistry blood sample	X	X	X	X		X		X		X	
Coagulation	X	If clinically indicated									
Urinalysis (dipstick)	X	X	X	X		X		X		X	
Prior/concomitant medications	From 28 days prior to day 1 until 130 days after EOT or start of new antineoplastic therapy, whichever is sooner. After start of a new antineoplastic therapy, only report concomitant medications for AEs/SAEs suspected to be related to study treatment.										

[redacted]

Period	Screening	Treatment		EOT		Safety Follow-up					EOS
Cycle		Cycle 1	Cycle 2								
Visit Name	Screening	Treatment C1D1	Treatment C2D1	EOT	Surgery	Safety Follow-up 1	Safety Follow-up 2	Safety Follow-up 3	Safety Follow-up 4	Safety Follow-up 5	EOS
Days	-28 to -1	1	22	When applicable[6]	4 to 6 weeks	From EOT: 26	From EOT: 52	From EOT: 78	From EOT: 104	From EOT: 130	-
Non-drug therapies and procedures	From 28 days prior to day 1 until 130 days after EOT or start of new antineoplastic therapy, whichever is sooner. After start of a new antineoplastic therapy, only report non-drug therapies for AEs/SAEs suspected to be related to study treatment.										
Adverse Events	Continuous, up to 130 days after last dose of study treatment. After starting a new antineoplastic therapy, only report AEs suspected to be related to study treatment.										
Serious Adverse Events	Continuous, up to 130 days after last dose of study treatment. After starting a new antineoplastic therapy only report SAEs suspected to be related to study treatment.										
Serum Pregnancy Test	X			X							
Urine Pregnancy Test[2]		S	S			S		S		S	
PET-CT (with diagnostic quality CT)	X			To be performed within 7 days prior to surgery							
CT/MRI - Thorax, Abdomen, Pelvis (if no diagnosis PET-CT captured)	X			To be performed within 7 days prior to surgery							
FDG-PET (If no diagnosis PET-CT captured)	X			To be performed within 7 days prior to surgery							
Brain MRI or CT with contrast	X			If clinically indicated							
Surgery					X						

[redacted]

Period	Screening	Treatment		EOT		Safety Follow-up					EOS
Cycle		Cycle 1	Cycle 2								
Visit Name	Screening	Treatment C1D1	Treatment C2D1	EOT	Surgery	Safety Follow-up 1	Safety Follow-up 2	Safety Follow-up 3	Safety Follow-up 4	Safety Follow-up 5	EOS
Days	-28 to -1	1	22	When applicable[6]	4 to 6 weeks	From EOT: 26	From EOT: 52	From EOT: 78	From EOT: 104	From EOT: 130	-
Tumor sample from surgery[1]					X						
MPR					X						
Canakinumab PK sampling		pre-dose	pre-dose	X		X		X		X	
Canakinumab Immunogenicity sampling		pre-dose	pre-dose	X		X		X		X	
Canakinumab Pharmacodynamic / Total IL-1β		pre-dose	pre-dose	X		X		X		X	
Pembrolizumab PK sampling		pre-dose and EOI	pre-dose	X		X					
Pembrolizumab Immunogenicity sampling		pre-dose	pre-dose	X		X					
Blood (serum) hs-CRP[3]		pre-dose	pre-dose	X[7]		X		X		X	
Blood (plasma) Cytokines panel including hsIL-6[4]		pre-dose	pre-dose	X[7]		X		Only hs-IL-6		Only hs-IL-6	
[redacted]											

[redacted]

Period	Screening	Treatment		EOT		Safety Follow-up					EOS
Cycle		Cycle 1	Cycle 2								
Visit Name	Screening	Treatment C1D1	Treatment C2D1	EOT	Surgery	Safety Follow-up 1	Safety Follow-up 2	Safety Follow-up 3	Safety Follow-up 4	Safety Follow-up 5	EOS
Days	-28 to -1	1	22	When applicable[6]	4 to 6 weeks	From EOT: 26	From EOT: 52	From EOT: 78	From EOT: 104	From EOT: 130	-
Drug Dispensation (Canakinumab)		X	X								
Drug Dispensation (Pembrolizumab)		X	X								
Trial Feedback Questionnaire		X		X							
IRT discontinuation				X							
Antineoplastic therapies since discontinuation of study treatment						X	X	X	X	X	
Safety Follow up Call							S		S		
Disposition Assessment	X			X							X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[1] Lymph nodes might be requested if collected
[2] For women with child bearing potential status confirmed only
[3] (5 ml) of whole blood will be collected for hs-CRP
[4] (10 ml) of whole blood will be collected for cytokines, except at Safety Follow Up visits at Day 78 and Day 130, (3ml) will be collected.

[redacted]

[6] Latest 21 days after permanently discontinuation of study treatment, but before the surgery
[7] Biomarker blood samples should be collected at the end of treatment but more specifically at time of surgery if possible, if not within 4 days prior to surgery

[redacted]

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 8-1 and Table 8-2). Laboratory parameters may be retested within the 28-day screening period for a subject if such parameters meet an exclusion criterion.

Histopathology status (squamous vs non-squmous) 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.

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 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

Following registering in the IRT for screening, subject eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer and comply with detailed guidelines in the IRT manual.

8.1.2 Information to be collected on screening failures

Subjects who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a SAE during the screening phase (see SAE section for reporting details). AEs 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 of the screen fail that the subject was not randomized.

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) and current medical condition

[redacted]

- Cancer characteristics including diagnosis, stage and grade of cancer
- Other assessments will be completed for the purpose of determining eligibility for inclusion in the study as reported in Table 8-2 (e.g. ECOG PS, complete physical examination, vital signs, body weight, hematology, blood chemistry, coagulation, urinalysis, serum pregnancy test for all female subjects, tumor imaging assessments).
- Prior and current concomitant medications and surgical and medical procedures.
- Tumor imaging assessments - Refer to Section 8.5.3.
- Tumor sample with histopathology assessment

  Data to be collected on Cycle 1 Day 1 pre-dose include:
  - 12-Lead ECG
  - PK, IG and PD

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with CRF. Participant race and ethnicity are collected to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

8.3 Efficacy

8.3.1 Tumor assessments

MPR: Response will be assessed centrally at the time of surgery (by number of subject with ≤10% residual viable tumor cells). For details please refer to Section 8.5.2.

Radiology tumor assessments: Will be assessed by investigator (RECIST 1.1) at screening and before surgery. For details please refer to Section 8.5.4 .

8.3.2 Appropriateness of efficacy assessments

Not Applicable.

8.4 Safety

Safety assessments are specified below and will be monitored by assessing physical examination, ECOG PS, vital signs, body weight, ECG, laboratory assessments, pregnancy tests, as well as collecting AEs at every visit. For details on AE collection and reporting, refer to AE section. All safety assessments should be completed as per Table 8-2.

Table 8-3 Assessments & Specifications

Assessment	Specification
Physical examination	At screening (within 10 days before cycle 1 day 1), a complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

[redacted]

Assessment	Specification
	After randomization (at C1D1 and all following visits) a short physical exam will include the examination of general appearance and vital signs (including blood pressure [SBP and DBP] and pulse). . Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs must include at minimum: systolic and diastolic blood pressure (supine position preferred when ECG is collected), respiratory rate, pulse rate and body temperature.
Height and weight	Height in centimeters (cm) or inches (in) and body weight (to the nearest 0.1 kilogram (kg) or pounds (lb) in indoor clothing, but without shoes) will be measured as specified in Table 8-2.
ECG	Local single 12-lead ECGs should be recorded at baseline prior to the dose administration, after the subject has been resting for 5-10 min.

Post-treatment discontinuation

All safety assessments (including pregnancy test for female subjects of child bearing potential) should be completed as per Table 8-2. 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. Data collected should be added to the appropriate eCRF.

8.4.1 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, chemistry, and other blood specimens (Table 8-1 and Table 8-2). 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).

More frequent timepoints should be added as deemed necessary per the investigator's judgment to make sure toxicity profile is sufficiently characterized and dose interruption 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

[redacted]

all laboratory reports for subjects in the study and evaluating any abnormalities for clinical significance.

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**
- Patient eligibility was confirmed 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.

Table 8-4 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils (absolute value preferred, %s are acceptable))
Chemistry	Albumin, ALP, ALT, AST, GGT, Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatinine clearance, Direct Bilirubin, Indirect Bilirubin (Only if TBIL is >= grade 2), TBIL, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, pancreatic amylase (as needed), Lipase, Glucose (*fasting*)
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	PT, International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Thyroid	T3 [free], T4 [free], TSH
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (baseline)
Infectious markers	Tuberculosis testing (as defined by country guidelines), HIV (where locally required)

[redacted]

Test Category	Test Name
Pregnancy Test	At screening visit and EOT, serum pregnancy test; if local requirements dictate otherwise, local regulations should be followed Urine pregnancy test (refer to 'Pregnancy and assessments of fertility' Section 8.4.3)

Hematology, chemistry, thyroid function tests, coagulation, urinalysis and infectious disease marker tests are to be performed according to the visit schedule (Table 8-2). Laboratory assessment done ≤ 3 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.

8.4.2 Electrocardiogram (ECG)

At cycle 1 Day 1 pre-dose, local single 12-lead ECGs should be recorded after the subject has been resting for 5-10 min as indicated in Table 8-2.

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.

8.4.3 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. 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). If local requirements dictate otherwise, local regulations should be followed.

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. (Section 10.1.4).

[redacted]

8.5 Additional assessments

8.5.1 Pharmacokinetics

8.5.1.1 Pharmacokinetics (PK), immunogenicity (IG) and pharmacodynamic (PD) assessments

To evaluate canakinumab and pembrolizumab exposure and immunogenicity in this indication, and also to evaluate exposure of the proposed dosing regimen, sample collections for analysis of PK and ADA are currently planned for canakinumab and pembrolizumab when administered alone and in combination.

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/IG/PD should be from a different site.

For all PK/IG/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 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. Refer to [Central Laboratory Manual] and flowchart for detailed PK, IG and PD collection for canakinumab, and PK, IG collection for pembrolizumab.

[redacted]

Timepoints of blood sample collection for canakinumab PK, IG and PD are outlined in Table 8-5.

Table 8-5 Blood collection schedule for canakinumab (s.c. injection, 200 mg Q3W) PK, IG and PD

Dose Reference Identification (ID)	PK sample number	IG sample number[b]	Total IL-1β (PD) sample number[b]	Scheduled timepoints (hours)		
				Cycle	Day	Scheduled time (hours)
101	1	11	21	1	1	0 h / pre-dose[a]
101/102*	2	12	22	2	1	504 h post dose / 0 h pre-dose[a]
	3	13	23	EOT	NA	Anytime

[redacted]

Dose Reference Identification (ID)	PK sample number	IG sample number[b]	Total IL-1β (PD) sample number[b]	Scheduled timepoints (hours)		
				Cycle	Day	Scheduled time (hours)
	4	14	24	safety follow-up 1 (26 days post-EOT)	NA	Anytime
	5	15	25	safety follow-up 3 (78 days post-EOT)	NA	Anytime
	6	16	26	safety follow-up 5 (130 days post-EOT)	NA	Anytime
	1001+[c]	2001+ [d]	3001+ [e]	NA	NA	Unscheduled

* The first Dose Reference ID is for last dose received prior to the collection of the PK sample, while the second Dose Reference ID is for the current dose

[a] Sample should be drawn within 24 hours prior to the next dose of canakinumab

[b] IG and PD samples are to be collected together with PK samples at the same time.

[c] PK sample numbers for any unscheduled PK collection will start with 1001, 1002, etc.

[d] IG sample numbers for any unscheduled IG collection will start with 2001, 2002 etc.

[e] PD sample numbers for any unscheduled PD collection will start with 3001, 3002 etc.

Timepoints of blood sample collection for pembrolizumab PK and IG are outlined in Table 8-6.

Table 8-6 Blood collection for pembrolizumab (30 min i.v. infusion, 200 mg Q3W) PK and IG

Dose Reference Identification (ID)	PK sample number	IG sample number[b]	Scheduled timepoints (hours)		
			Cycle	Day	Scheduled time (hours)
201	31	41	1	1	0 hr / pre-infusion[a]
201	32		1	1	EOI (within 30 min)
201/202*	33	42	2	1	504 h post-dose / 0 hr pre-infusion[a]
	34	43	EOT	NA	Anytime
	35	44	safety follow-up 1 (26 days post-EOT)	NA	Anytime
	4001+[c]	5001+[d]	NA	NA	Unscheduled

EOI = end of infusion

* The first Dose Reference ID is for last dose received prior to the collection of the PK sample, while the second Dose Reference ID is for the current dose

[redacted]

Dose Reference Identification (ID)	PK sample number	IG sample number[b]	Scheduled timepoints (hours)		
			Cycle	Day	Scheduled time (hours)

[a] Sample should be drawn within 24 hours prior to the next infusion of pembrolizumab
[b] IG samples are to be collected together with PK samples at the same time.
[c] PK sample numbers for any unscheduled PK collection will start with 4001, 4002 etc.
[d] IG sample numbers for any unscheduled IG collection will start with 5001, 5002 etc.
Note: PK/IG samples are collected from the arm opposite from infusion site.

8.5.2 Biomarkers

The biomarker analysis will investigate whether the mutations [redacted] of the tumor and its microenvironment are associated with the effect of canakinumab treatment. The analysis will be performed in tumor samples collected both at baseline and at the time of resection as well as in non-invasive blood samples collected at screening/baseline, on treatment, end of treatment and after treatment. Such assessments will provide information on whether the [redacted] tumor is predictive of MPR and identify changes to the tumor microenvironment following treatment.

Primary and secondary endpoints (MPR assessment) in tumor samples collected at time of resection

The primary endpoint is the MPR rate as assessed by the number of subjects with ≤ 10% residual viable cancer cells. The primary endpoint for MPR will be assessed centrally, the secondary endpoint for MPR will be assessed locally based on all randomized subjects based on local review in each treatment arm. All formalin-fixed, paraffin embedded (FFPE) tumor tissues collected at surgery must be submitted, detailed instructions for sample collection and processing will be included in the central lab manual.

Secondary endpoint [redacted] assessments in tumor biopsy samples collected at baseline and at time of resection

Mandatory tumor samples are to be collected at screening and may include core, excisional and incisional biopsies. Fine needle aspirates are not acceptable sample types. A FFPE tumor block is to be submitted and if not available, a minimum of 25 slides must be submitted (the slide cut date must be within 5 months of first day of study treatment, and must be included on the requisition form). Lymph nodes resected and available will also be requested. These will be used to assess the immune cell activation status.

Assessments for secondary endpoints will include the IHC immune markers PD-L1 and CD8. [redacted]

Secondary endpoint [redacted] assessments performed using non-invasive samples

Mandatory blood samples will be collected at baseline, on treatment, at the end of treatment (but more specifically at time of surgery if possible, if not within 4 days prior to surgery) and after treatment (these samples will be collected only if no new antineoplastic has been started).

[redacted]

Assessments for secondary endpoints will include hs-CRP and hs-IL-6. [redacted]

[redacted]

8.5.3 Imaging

Tumor response will be assessed locally by the investigator according to the Novartis guideline version 3.2 based on RECIST 1.1 (Section 16.3).

Imaging collection is required at baseline and before the surgery, please see Assessment schedule Table 8-2.

PET and diagnostic quality CT imaging are required at both visits in order to support the study endpoints. The CT component of the PET-CT may be used in lieu of standalone CT/MRI only if the CT component is of similar diagnostic quality to a contrast enhanced CT performed without PET. Contrast enhancement should be used for all imaging unless contraindicated for the subject.

These guidelines distinguish a diagnostic quality (optimized) CT exam from an exam performed to serve solely as the attenuation correction map for the PET exam:

1. The CT should be performed with a standard x-ray dose
    1. For an adult of average size, a minimum tube current of ≥100mAs
    2. A dose modulated mAs is acceptable if it falls within diagnostic range
2. The CT should be performed with IV or oral contrast unless medically contraindicated
3. Other factors, such as subject arm positioning (arms raised preferred), field of view and breath holding technique (mid-inspiration preferred) should be performed with dedicated CT technique

The possible scanning scenarios (in addition to Brain MRI or CT brain with contrast as outlined in the assessment schedule) are:

1. PET-CT with diagnostic quality CT component
2. PET-CT with non-diagnosis CT + dedicated CT/MRI
3. Dedicated CT/MRI + dedicated FDG-PET

The same scanning method and parameters should be used at Screening and before Surgery. If independent PET and CT scans are used, and both are done on the same day, the PET must be performed prior to the contrast-enhanced CT as to not compromise PET results.

[redacted]

Screening/baseline assessment:

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.

End of treatment assessment:

Imaging assessment will be performed within 7 days prior surgery.

Unscheduled assessment:

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.

8.5.4 Other Assessments

8.5.4.1 Trial Feedback Questionnaire (TFQ)

This trial will include an option for patients to complete an anonymized questionnaire, TFQ for subjects to provide feedback on their clinical trial experience. Individual subject level responses will not be reviewed by investigators. Responses would be used by the sponsor (Novartis) to understand where improvements can be made in the clinical trial process. This questionnaire does not collect data about the subject's disease, symptoms, treatment effect or AEs and therefore would not be trial data.

8.5.4.2 Surgery related information

The surgery should be performed as per local guidelines/clinical practice. The following surgery instructions are general recommendations and should only be considered as a guidance.

- Mediastinal lymph node staging by endobronchial ultrasound or mediastinoscopy is encouraged.
- Resection may be accomplished by open or minimally invasive techniques (i.e. clamshell or hemiclamshell incision, robot assisted thoracic surgery, sternotomy, thoracotomy, or video assisted thoracic surgery/thoracoscopy).
- Pathologic complete resection of the primary tumor (R0 resection) should be performed. Anatomic resection by bilobectomy, lobectomy, pneumonectomy, or segmentectomy is strongly preferred. Wedge (nonanatomic) resection can be done for very small (2 cm or less) tumors located peripherally where at least a 1 cm margin in all directions is possible.
- Hilar and mediastinal lymph node dissection or sampling should be performed. For right sided resections, lymph nodes for levels 4R, 7, 10R, and 11R, and for left sided resections lymph nodes from levels 5/6, 7, 10L, and 11L should be dissected or sampled.

[redacted]

Surgery related information, including safety-related, will be collected on the appropriate eCRF page.

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, 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.

Study treatment must be discontinued under the following circumstances :

- Subject/guardian decision
- Physician decision
- Pregnancy
- Any situation in which study participation might result in a safety risk to the subject
- Study terminated by sponsor

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information. The investigator must register the subject's discontinuation from study treatment in the IRT system.

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 (see Section 7). **Where possible, they should return for the assessments as 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.

All subjects will have an EOT visit once all drugs of the study treatment are permanently discontinued (canakinumab and/or pembrolizumab as applicable). Subjects should be scheduled for an EOT visit latest 21 days after permanent discontinuation of study treatment but before the surgery, at which time all assessments listed for EOT visit will be performed (Table 8-2). 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 randomized subjects will be followed for AEs and SAEs for at least 130 days following the last dose of study treatment. Subjects will complete a

[redacted]

total of five safety follow-up visits every 26 days until 130 days after end of treatment visit, during these safety follow-up visits additional assessments and blood samples will be collected as indicated in the Visit Evaluation Schedule (VES) (Table 8-2). The information collected is kept in source documentation and in eCRF (Table 8-2). 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.

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

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 his/her consent and record this information.

Where consent to the use of personal and coded data is not required, the participant cannot withdraw consent but still retains the right to object to the further use of personal data.

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.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 8-2).

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

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

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

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, 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

[redacted]

diligence has been completed. Subjects lost to follow up should be recorded as such on the appropriate eCRF page.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. 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 (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject (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 the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their last safety follow-up visit at 130 days after end of treatment visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

Novartis will not supply study treatment to subjects after surgery. All randomized subjects should have the last safety follow-up visit conducted 130 days after end of treatment visit. The information collected is kept as source documentation. 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.

Primary analysis will be performed after all subjects have had surgical resection or have discontinued study treatment earlier due to any reason. The primary analysis data will be summarized in the primary clinical study report (CSR). Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing subjects will continue with safety follow-up assessments as per the schedule of assessments (Table 8-2).

The end of study defined as the earliest occurrence of one of the following: all subjects have completed or discontinued from the study.

The final analysis will occur at the end of the study. All available data from all subjects up to this cut-off date will be analyzed and summarized in a final CSR.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom 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.

The investigator has the responsibility for managing the safety of individual subject and identifying AEs.

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

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs 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.

AEs must be recorded 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. AEs will be assessed and graded according to the Common Terminology Criteria (CTC) for AEs (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 (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment

All AEs must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/withdrawn

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

[redacted]

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

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued for at least 130 days following the last dose of study treatmentOnce 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 SAE, except if the investigator considers that progression of malignancy is related to study treatment.

AEs separate from the progression of malignancy (i.e. 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 IB.

Abnormal laboratory values or test results constitute AEs 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

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.

AESI are defined on the basis of an ongoing review of the safety data.

AESI for canakinumab include:

- Infections/Opportunistic infections
- Neutropenia

[redacted]

- 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 AEs 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 AE (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

[redacted]

do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

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 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 SAE 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 130 days after the last administration of study treatment or the start of a new post study treatment antineoplastic medication, whichever comes first must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Note: Any SAEs experienced after the 130-day safety follow-up period or after the start of a new post study treatment antineoplastic medication should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment.

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 within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Novartis Chief Medical Office & Patient Safety (CMO&PS) department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an IN to inform all

[redacted]

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 (ECs) in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor 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 the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a pregnancy occurs while on study, the newborn will be followed for at least 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 recorded on the appropriate CRF irrespective of whether or not associated with an 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 Dosing CRF (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

[redacted]

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

10.2 Additional Safety Monitoring

Not applicable.

10.2.1 Steering Committee

The Steering Committee (SC) will be established comprising investigators participating in the trial, i.e. not being members of Novartis 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 eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (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 (recorded on CRFs) (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.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Data collected by third parties (hematology, biochemistry, biomarkers, ECG, MPR and PK) will be sent electronically to Novartis.

11.2 Database management and quality control

Novartis personnel (or designated contract research organisation (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 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 AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive 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, it will be locked 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.

After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

11.3 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 GCP, 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. Continuous remote monitoring of each site's data may be performed by a Novartis/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original ICF 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 CRFs are performed according to the

[redacted]

study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The primary efficacy analysis will be performed after all subjects have had surgical resection or have discontinued study treatment earlier due to any reason.

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

The FAS comprises 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, to which they have been assigned to during the randomization procedure.

12.1.2 Safety set

The Safety Set includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, either canakinumab and/or pembrolizumab, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

12.1.3 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (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 Statistical Analysis Plan (SAP). PAS will be defined for canakinumab and pembrolizumab separately.

12.1.4 Other analysis sets

Other analysis sets, if needed, will be specified in the SAP.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS and Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

[redacted]

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure for study treatment and for each study drug (canakinumab and pembrolizumab) will be presented. The dose intensity and relative dose intensity will be summarized for each study drug components by descriptive statistics.

The number of subjects with dose adjustments (interruption, or permanently 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)

The primary objective of the study is to assess the rate of MPR (≤ 10% residual viable tumor) per central review at the time of surgery in canakinumab alone and in combination with pembrolizumab treatment arms.

12.4.1 Definition of primary endpoint(s)

The primary endpoint is MPR rate, defined as the percentage of subjects with ≤ 10% residual viable cancer cells. MPR will be assessed in FAS per central review.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint analysis will be described by the following five attributes:

1. The **target population** is defined as all randomized patients who are histologically confirmed NSCLC stage IB-IIIA (per AJCC 8th edition), deemed suitable for primary resection by treating surgeon, except for N2 and T4 tumors.
2. The **primary variable** is the percentage of subjects with a major pathological response (defined as ≤ 10% residual viable cancer cells per central review). Any patient who has >10% residual viable cancer cells, or starts new antineoplastic therapy medication prior to surgery, or does not have the surgery performed, is considered as a non-responder.
3. The **study treatment** is canakinumab as monotherapy or in combination with pembrolizumab.
4. The **intercurrent events** of interest in this study are: start of new antineoplastic therapy prior to surgery and discontinuation of study treatment prior to surgery. These intercurrent events will be addressed as follows:
   a. **Start of new antineoplastic therapy prior to surgery**: subject will be considered as non-responder (composite strategy)
   b. **Discontinuation of study treatment prior to surgery:** subject will be included in the analysis regardless of this intercurrent event (treatment-policy strategy).
5. The **summary measure** is MPR rate with its corresponding two-sided exact binomial 95% confidence interval (Clopper and Pearson E. 1934) in canakinumab alone arm and canakinumab in combination with pembrolizumab arm.

[redacted]

A MPR of approximately 20% can be achieved using chemotherapy (Pataer 2012). For canakinumab alone arm, a 10% absolute improvement in the MPR to 30% is considered a clinically meaningful minimum improvement in this study population. Therefore, proof of efficacy in canakinumab alone arm will be declared if both of the following conditions are met:

- the mean of the posterior distribution of MPR is at least 30% and
- the posterior probability that the MPR is ≥ 20% is at least 90%

For the combination of canakinumab and pembrolizumab treatment arm, a 25% absolute improvement in the MPR to 45% is considered a clinically meaningful minimum improvement in this study population. Therefore, proof of efficacy in the combination treatment arm will be declared if both of the following conditions are met:

- the mean of the posterior distribution of MPR is at least 45% and
- the posterior probability that the MPR is ≥ 30% is at least 90%

The posterior distribution of MPR will be derived from the prior distribution and all available data from the subjects included in the FAS. A minimally informative unimodal Beta prior (Neuenschwander et al 2008) will be used for MPR in each arm. Details of prior distribution will be specified in the SAP.

12.4.3 Handling of missing values/censoring/discontinuations

Refer to Section 12.4.2 for details on handling of intercurrent events.

Subjects who have an unknown MPR status due to surgery not being performed (including lost to follow-up or withdrawal of study consent before surgery) will be considered as non-responders when estimating MPR rate.

12.4.4 Supportive analyses

Additional supportive analysis for the primary analysis of MPR rate will be conducted by using an alternative strategy in handling of the intercurrent events.

The target population, the primary variable and the summary measure will be the same as for the primary endpoint analysis. For the intercurrent event of start of new antineoplastic therapy prior to surgery: subjects will be included in the analysis regardless of this intercurrent event (treatment-policy strategy).

12.5 Analysis of secondary endpoints

12.5.1 Efficacy endpoints

MPR rate will be assessed using the same patient population used in the primary analysis, including the strategy for handling intercurrent events (1) based on local review in all three treatment arms and (2) based on central review in pembrolizumab monotherapy arm.

MPR rate for all the above specified analyses will be summarized by treatment arm along with the two-sided exact binomial 95% confidence interval (Clopper and Pearson E. 1934).

The difference in MPR rate between canakinumab in combination with pembrolizumab and pembrolizumab single agent arm along with the two-sided exact 95% confidence interval based on Chan and Zhang (1999) will be summarized based on central review using the same patient

[redacted]

population used in the primary analysis, including the strategy for handling intercurrent events. The posterior probability of the difference 10% or greater in MPR rate will also calculated.

Surgical feasibility rate is defined as the percentage of subjects in FAS who undergo surgery following study treatment. Surgical feasibility rate and two-sided exact binomial 95% confidence interval (Clopper and Pearson E. 1934) will be presented by treatment group.

ORR is defined as the percentage of subjects in FAS with a best overall response of CR or PR, as per local review. The best overall response will be the observed response at the assessment performed on the EOT visit prior to surgery. ORR will be evaluated according to RECIST 1.1 (see Section 16.3 for details). ORR and two-sided exact binomial 95% confidence interval (Clopper and Pearson E. 1934) will be presented by treatment group. Subjects with a best overall response (BOR) of 'Unknown' per RECIST 1.1 will be considered as non-responders when estimating ORR.

12.5.2 Safety endpoints

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

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 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 study medication
2. On-treatment period: from day of first dose of study medication to 130 days after last dose of study medication
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 AEs will include only AEs that started or worsened during the on-treatment period, the treatment-emergent AEs.

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

SAE, non-serious AEs and 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 SAEs (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.

[redacted]

12.5.2.2 Clinical laboratory evaluations

Grading of laboratory values will be assigned programmatically as per NCI CTCAE version 5.0. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account.

CTCAE v5.0 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 might be specified in the analysis plan.

12.5.2.3 Other safety evaluations

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/cycle. Notable values will be flagged.

Immunogenicity

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

12.5.3 Pharmacokinetics

PAS will be used in the pharmacokinetic data analysis. Descriptive statistics (n, m (number of non-zero concentrations), mean, coefficient of variation in percent (CV%), SD, median, geometric mean, geometric CV%, minimum and maximum) for canakinumab and pembrolizumab concentrations will be presented at each scheduled timepoint separately.

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

[redacted]

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 posthoc 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 to determine the effects of canakinumab on pembrolizumab.

12.5.4 Biomarkers

The secondary objective related to biomarker is to assess the relationship between key blood or tissue based biomarkers and MPR. FAS will be used for biomarker related analyses.

The relationship between key IHC markers (PD-L1, CD8), key cytokines (hs-CRP and hs-IL-6) assessed at baseline and post-baseline and MPR will be explored. MPR will be summarized by treatment arm and subgroup along with the two-sided exact binomial 95% confidence interval (Clopper and Pearson E. 1934). The threshold used for the markers will be specified in SAP. In addition, baseline and changes from baseline for the IHC markers and cytokines (absolute change, percent change and fold change) at each time point 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.

All biomarker data will also be listed.

[redacted]

[redacted]

12.7 Interim analyses

Not applicable.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

A MPR of approximately 20% can be achieved using chemotherapy (Pataer 2012). A 10% absolute improvement to 30% and a 25% absolute improvement to 45% in MPR rate are considered clinically meaningful minimum improvement in canakinumab alone arm and canakinumab in combination with pembrolizumab arm, respectively.

Approximately 110 subjects will be randomized in a 2:2:1 ratio to one of the treatment arms (canakinumab alone or canakinumab in combination with pembrolizumab or pembrolizumab alone). The proof of efficacy in each treatment arm will be determined by Bayesian double criteria.

Among the 44 subjects randomized to canakinumab single agent treatment, at least 14 responders are needed to meet the proof of efficacy criteria. When the true MPR rate is $\leq 20\%$, the probability of erroneously declaring proof of efficacy is at most 4.4%, while the probability of declaring proof of efficacy is at least 89.8% for MPR $\geq 40\%$ (Table 12-1).

Among the 44 subjects randomized to the canakinumab and pembrolizumab combination treatment, at least 20 responders are required to meet the proof of efficacy criteria. When the true MPR rate is $\leq 30\%$, the probability of erroneously declaring proof of efficacy is at most 2.1% while the probability of declaring proof of efficacy is at least 92.2% for MPR $\geq 55\%$ (Table 12-2). Assuming an enrollment rate of 6 subjects per month, the enrollment will be completed at approximately 18 months and MPR assessment for the last patient randomized will occur at approximately 20 months from the date of first subject randomized in the study.

[redacted]

Table 12-1 Operating characteristics with 44 subjects randomized to canakinumab treatment arm

True MPR	Probability of declaring proof of efficacy (14 or more responders)	Probability of missing proof of efficacy (13 or less responders)
20%	4.4%	95.6%
30%	45.2%	54.8%
40%	89.8%	10.2%
50%	99.5%	0.5%

Table 12-2 Operating characteristics with 44 subjects randomized to the canakinumab + pembrolizumab combination treatment arm

True MPR	Probability of declaring proof of efficacy (20 or more responders)	Probability of missing proof of efficacy (19 or less responders)
30%	2.1%	97.8%
40%	27.7%	72.3%
45%	53.4%	46.6%
55%	92.2%	7.8%

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 GCP, 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 IRB/IEC for the trial protocol, written ICF, 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

[redacted]

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.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

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 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 Standard Operating Procedures (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

[redacted]

study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Pembrolizumab Dose Modification Guidelines

Table 16-1 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 be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.** **3. For severe and life-threatening irAEs, IV corticosteroid should be initiated 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 recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg	• Monitor participants for signs and symptoms of enterocolitis (ie,
	Grade 4	Permanently discontinue		

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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 be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.** **3. For severe and life-threatening irAEs, IV corticosteroid should be initiated 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**
			prednisone or equivalent) followed by taper	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

[redacted]

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 be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.** **3. For severe and life-threatening irAEs, IV corticosteroid should be initiated 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**
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 returned to baseline or is stable).
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (TIDM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence 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.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including
	Grade 3 or 4	Withhold or permanently discontinue[1]		

[redacted]

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 be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.** **3. For severe and life-threatening irAEs, IV corticosteroid should be initiated 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**
				hypopituitarism and adrenal insufficiency)
Hyperthyroidism	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]		
Hypothyroidism	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 (initial 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		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold		

[redacted]

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 be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered.** **3. For severe and life-threatening irAEs, IV corticosteroid should be initiated 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	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis	• Based on type and severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[redacted]

16.2 Appendix 2: Medications to be used with caution with canakinumab while on study

Table 16-2 CYP3A substrates with narrow therapeutic index, or sensitive CYP2C9 substrates with 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, October 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).

[redacted]

16.3 Appendix 3: Guidelines for Response, Duration of Overall Response, TTF, TTP, Progression-Free Survival, and Overall Survival (based on RECIST 1.1)

16.3.1 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 16.3.2 and the definition of best response in Section 16.3.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 16.3.3.2 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 16.3.4 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.

16.3.2 Efficacy assessments

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

16.3.2.1 Definitions

16.3.2.1.1 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 16.3.3.2.9

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

[redacted]

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.

16.3.2.1.2 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 16.3.3.2.9.

16.3.2.2 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.

[redacted]

- **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.

16.3.2.3 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 16.3.2.1.1
- **Nodal target:** See Section 16.3.2.1.1. 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.

[redacted]

16.3.2.4 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 16-3) and non-target lesions (Table 16-4) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 16-5) as well as the presence or absence of new lesions.

16.3.2.4.1 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.

[redacted]

16.3.2.4.2 Determination of target lesion response

Table 16-3 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 16.3.2.2).

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 16-3 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

[redacted]

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 CRF 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 CRF, 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.

[redacted]

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.

16.3.2.4.3 Determination of non-target lesion response

Table 16-4 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 16.3.2.4.3 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

[redacted]

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

16.3.2.4.4 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 16.3.2.5).
- 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 16.3.2.2.

16.3.2.5 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 16-5.

Table 16-5 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

[redacted]

Target lesions	Non-target lesions	New Lesions	Overall lesion response
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 16.3.2.4

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.

16.3.3 Efficacy definitions

The following definitions primarily relate to subjects who have measurable disease at baseline. Section 16.3.3.2.9 outlines the special considerations that need to be given to subjects with no measurable disease at baseline in order to apply the same concepts.

16.3.3.1 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

[redacted]

- 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.

[redacted]

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 et al (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).

[redacted]

16.3.3.2 Time to event variables

16.3.3.2.1 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.

16.3.3.2.2 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.

16.3.3.2.3 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.

16.3.3.2.4 PFS2

A recent EMA Guidelines, 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

[redacted]

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.

16.3.3.2.5 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.

16.3.3.2.6 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).

[redacted]

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.

16.3.3.2.7 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 16.3.3.2.6. 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.

16.3.3.2.8 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

[redacted]

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 16.3.3.2.8).

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 EOT 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.

[redacted]

16.3.3.2.9 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 16-6.

Table 16-6 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 16.3.2.4		

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.

16.3.3.2.10 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

[redacted]

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 16.3.3.2.8, and using the FDA guideline on endpoints (Section 16.3.5) as a reference, the following analyses can be considered:

Table 16-7 Options for event dates used in PFS, TTP, duration of response

Situation		**Options for end-date (progression or censoring)[1]** **(1) = default unless specified differently in the protocol or RAP**	**Outcome**
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	Progression or death after exactly one missing assessment	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	Progression or death after two or more missing assessments	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) 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)	As per above situations Censored Censored Event

[redacted]

Situation		Options for end-date (progression or censoring)[1] **(1) = default unless specified differently in the protocol or RAP**	Outcome
		(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	
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 16.3.3.2.8 2 =After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 16.3.3.2.8. 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

[redacted]

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 16-7 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.

16.3.4 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).

16.3.4.1 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.

[redacted]

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).

16.3.4.2 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 EOT visit and its associated assessments should occur within 21 days of the permanent discontinuation of study treatment but before the surgery.

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

- AE(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.

16.3.4.3 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:

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

[redacted]

- Death
- Progressive disease
- Study terminated by the sponsor

16.3.4.4 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.

16.3.4.5 Programming rules

The following should be used for programming of efficacy results:

16.3.4.5.1 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.

16.3.4.5.2 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

[redacted]

assessment date is calculated as outlined in Section 16.3.3.2.8). 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.

16.3.4.5.3 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.

16.3.4.5.4 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)'.

16.3.4.5.5 Study / project specific programming

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

16.3.4.5.6 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 16-7)
- 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 16.3.3.2.8. 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:

[redacted]

- 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.

16.3.5 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.

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FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

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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.

[redacted]

16.4 Appendix 4: NSCLC staging according to AJCC 8th edition

Figure 16-1 NSCLC staging: AJCC 8th edition

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Note:

Subjects with histological stage within the red box will be eligible.

N2, T4 and N2+ T4 subjects are not eligible.

[redacted]